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(54) Title: PROCESS FOR PREPARATION OF PALBOCICLIB

FIG. 1A

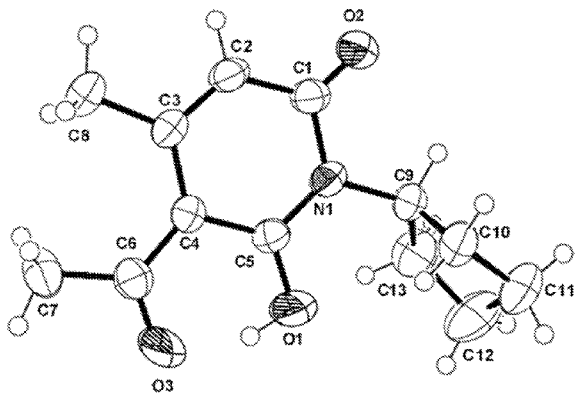
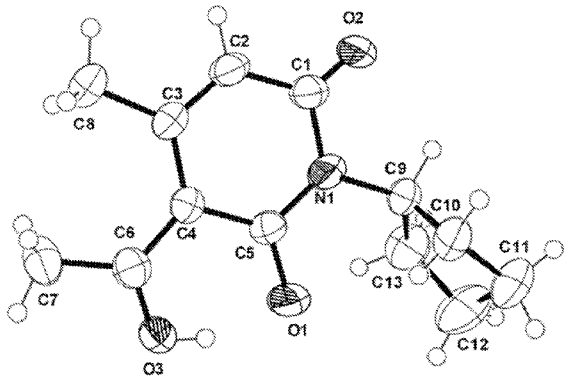


FIG. 1B



(57) Abstract: The present invention relates to improved processes for the preparation of palbociclib. The invention further provides intermediates and processes for the preparation of intermediates useful for the preparation of palbociclib.

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PROCESS FOR PREPARATION OF PALBOCICLIB

BACKGROUND OF THE INVENTION

Field of the invention

The present invention relates to improved processes for the preparation of palbociclib. The invention further provides intermediates and processes for the preparation of intermediates useful for the preparation of palbociclib.

Description of the Related Art

Cyclin-dependent kinases (CDKs) are important cellular enzymes that perform essential functions in regulating eukaryotic cell division and proliferation. CDK inhibitors may be useful for the treatment of proliferative disorders, including cancer.

Palbociclib, 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2ylamino)-*8H*-pyrido[2,3-*d*]pyrimidin-7-one, is a CDK4/6 inhibitor for use in the treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy or fulvestrant with disease progression following endocrine therapy.

Palbociclib and salts thereof are described in U.S. Patent Nos. 6,936,612, 7,456,168 and RE 47,739. Processes for the preparation of palbociclib, including salts and intermediates for the preparation thereof, are described in U.S. Patent No. 7,781,583 and International Publication No. WO 2008/032157. The preparation of palbociclib salts, and crystalline forms of such salts, is described in U.S. Patent Nos. 7,345,171 and 7,863,278. Solid forms of palbociclib are described in U.S. Patent No, 10,723,730 and International Publication No. WO 2014/128588. Formulations of palbociclib are described in U.S. Patent Publication No. 2018/0207100 and International Publication No. WO 2019/053650. The contents of each of the foregoing are incorporated herein by reference in their entirety.

A commercial route for manufacturing palbociclib has been described in: Duan et al., Palbociclib Commercial Manufacturing Process Development. Part I: Control of Regioselectivity in Grignard-Mediated S_NAr Coupling, Org. Process Research and Development, 20, 1191-1202 (2016); Maloney et al., Palbociclib Commercial Manufacturing Process Development. Part II: Regioselective Heck Coupling with Polymorph Control for Processability, Org. Process Research and Development, 20, 1203-1216 (2016); and Chekal et al., Palbociclib Commercial Manufacturing Process

Development. Part III. Deprotection Followed by Crystallization for API Particle Property Control, Org. Process Research and Development, 20, 1217-1226 (2016).

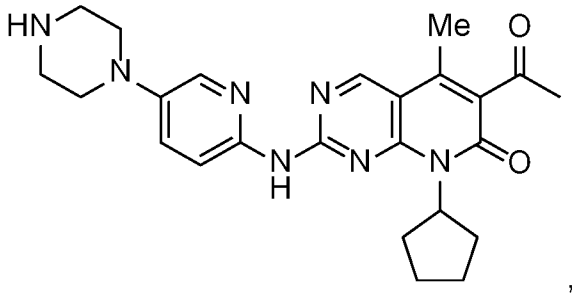
Alternative methods for the preparation of palbociclib, or intermediates for preparation thereof, have been reported in Chinese Patent Nos. 104478874, 106565707, 106608876 and 110016023, Chinese Patent Application Nos. 105418603 and 106565707, Indian Patent Application Nos. 201641043500, 201721023027 and 201741030232, U.S. Patent Publication No. 2017/0217962, U.S. Patent No. 10,807,978 and International Publication No. WO 2016/030439.

Improved processes for the preparation of palbociclib, and intermediates for the preparation thereof, that are cost-efficient, scaleable, high yielding, environmentally friendly and sustainable are highly desirable.

BRIEF SUMMARY OF THE INVENTION

The present invention provides improved processes for the preparation of palbociclib, or a salt thereof, including a pharmaceutically acceptable salt thereof, and intermediates useful for the preparation of palbociclib.

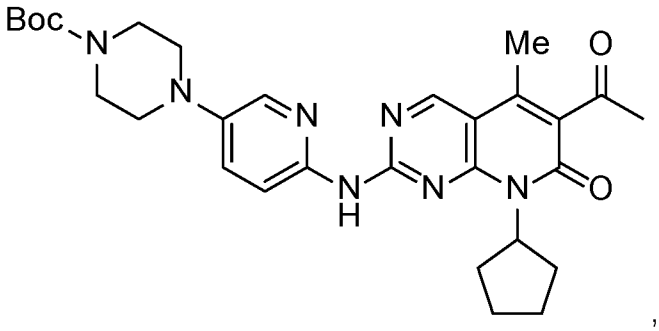
In one aspect, the invention provides a process for the preparation of palbociclib:



,

comprising:

(a) reacting the compound of Formula (I) prepared by the process of any of the embodiments described herein:



,

(I)

with formic acid; and

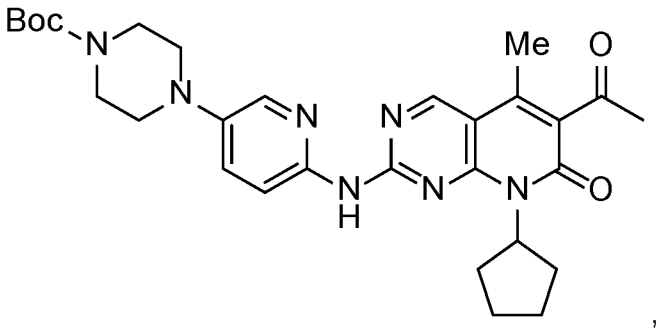
(b) diluting the reaction mixture with water, washing the aqueous layer with one or more organic solvents, and then adjusting the pH of the aqueous phase to basic pH with base to provide palbociclib (free base).

In preferred embodiments, the process further comprises: (c) cooling the mixture in step (b) to provide a slurry and filtering to isolate palbociclib.

In a preferred embodiment, the mixture of formic acid and the compound of Formula (**I**) in step (a) is heated to about 40°C under nitrogen atmosphere until completion of reaction. In a preferred embodiment, step (b) comprises washing the aqueous phase with one or more suitable organic solvents (such as CH_2Cl_2, EtOAc, *i*-PrOAc or Anisole) at elevated temperature (preferably about 50-65°C), and adjusting the pH of the aqueous layer to about pH 12.5 with aqueous base (preferably aq. sodium hydroxide) at elevated temperature, preferably about 40°C.

In a preferred embodiment, the process further comprises: (c) isolating palbociclib by gradually cooling the resulting slurry in step (b) to about 15°C and then filtering and washing the solid material with water; and optionally (d) drying the solid material under vacuum at about 25°C to obtain palbociclib.

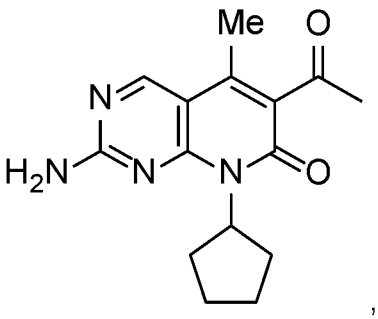
In one aspect, the invention provides a process for the preparation of a compound of Formula (I):



(I)

comprising:

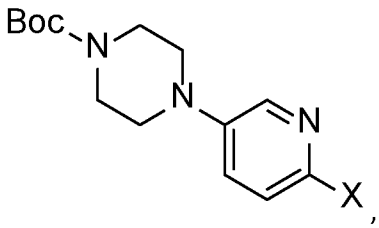
(a) coupling a compound of Formula (II) prepared by the process of any of the embodiments described herein:



(II)

or a salt thereof,

with a compound of Formula (III):

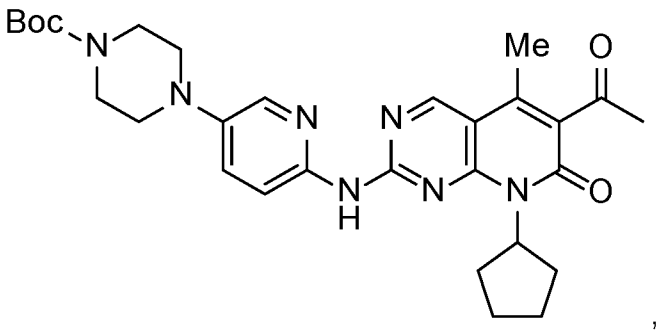


(III)

where X is a leaving group selected from a halo or a sulfonate ester,

in the presence of a transition metal catalyst, a base, and optionally a ligand, in a suitable solvent, to provide the compound of Formula (I).

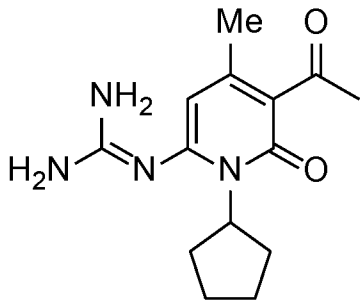
In another aspect, the invention provides a process for the preparation of a compound of Formula (I):



(I)

comprising:

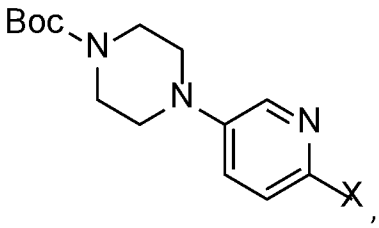
(a) coupling a compound of Formula (IV) prepared by the process of any of the embodiments described herein:



(IV)

or a salt thereof,

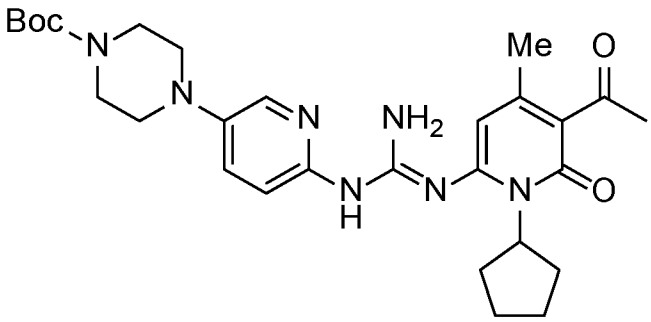
with a compound of Formula (III):



(III)

where X is a leaving group selected from a halo or a sulfonate ester,

in the presence of a transition metal catalyst, a base, and optionally a ligand, in a suitable solvent, to provide a compound of Formula (V):



; and

(V)

(b) reacting the compound of Formula (V) with a formylation reagent in a suitable solvent under dehydrative conditions to provide the compound of Formula (I), wherein the formylation reagent is a di(C_1-C_4 alkyl)formamide di(C_1-C_4 alkyl) acetal or a tri(C_1-C_4 alkyl) orthoformate.

The Boc-protected compound of Formula (I) may be converted to palbociclib, or a salt thereof, as further described herein or as known in the art.

In another aspect, the invention provides palbociclib, or a salt thereof, prepared according to any of the processes of the invention provided herein.

These and other aspects and embodiments of the invention are described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows ORTEP diagrams of the molecular structure of hydroxypyridone (VI) as a 50:50 mixture of tautomer (VI-a) (A) and tautomer (VI-b) (B).

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following detailed description of the preferred embodiments of the invention and the Examples included herein. It is to be understood that the terminology used herein is for the purpose of describing specific embodiments only and is not intended to be limiting. It

is further to be understood that unless specifically defined herein, the terminology used herein is to be given its traditional meaning as known in the relevant art.

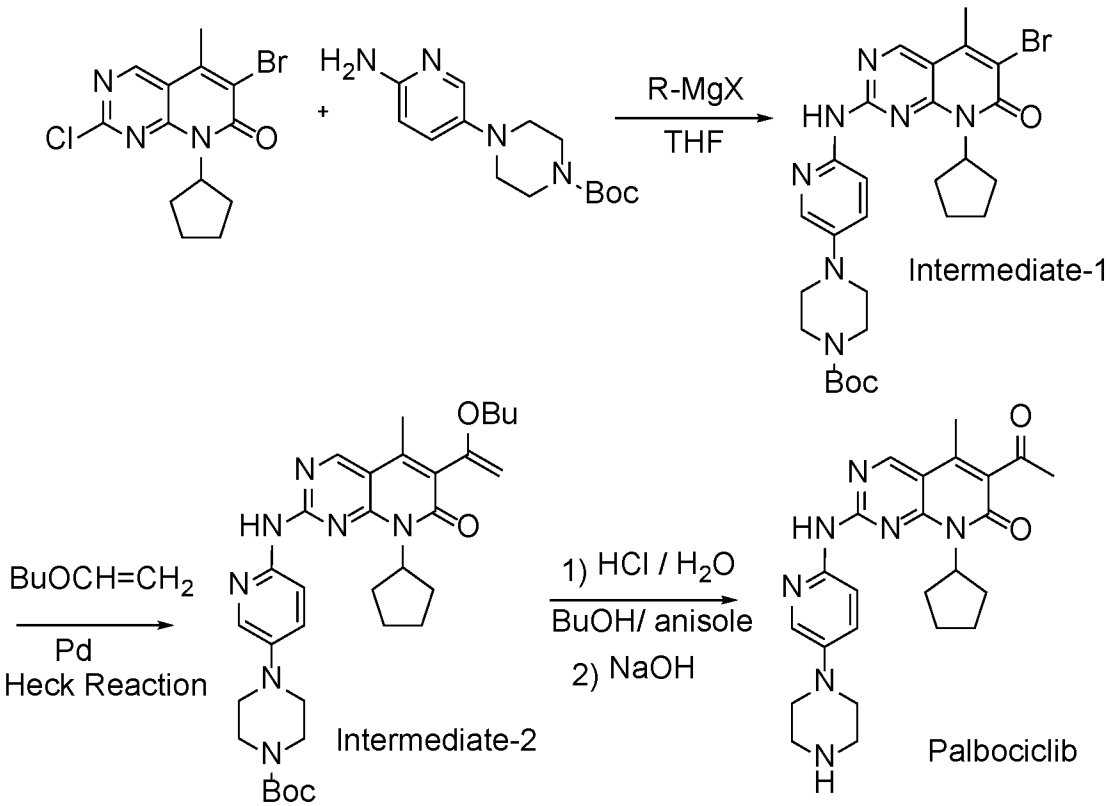
As used herein, the singular form "a", "an", and "the" include plural references unless indicated otherwise. For example, "a" suitable solvent may include one or more suitable solvents (i.e., a suitable solvent mixture).

The term "about" means having a value falling within an accepted standard of error of the mean, when considered by one of ordinary skill in the art, e.g., within plus or minus (±) 10% of the stated value.

The invention described herein suitably may be practiced in the absence of any element(s) not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms.

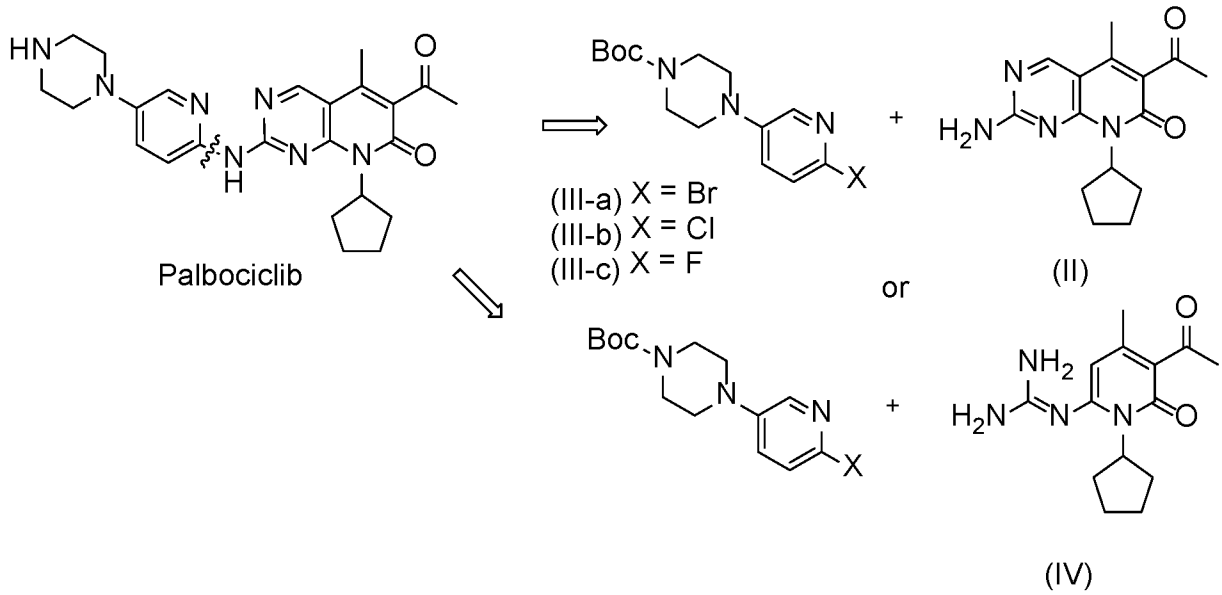
The current commercial route to palbociclib (Scheme 1) involves coupling 6-bromo-2-chloro-8-cyclopentyl-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one with tert-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate to give Intermediate-1, followed by Heck reaction with butyl vinyl ether to give Intermediate-2. Deprotection of Intermediate-2 by treatment with acid hydrolyzes the enol ether and removes the Boc-protecting group, providing palbociclib.

Scheme 1



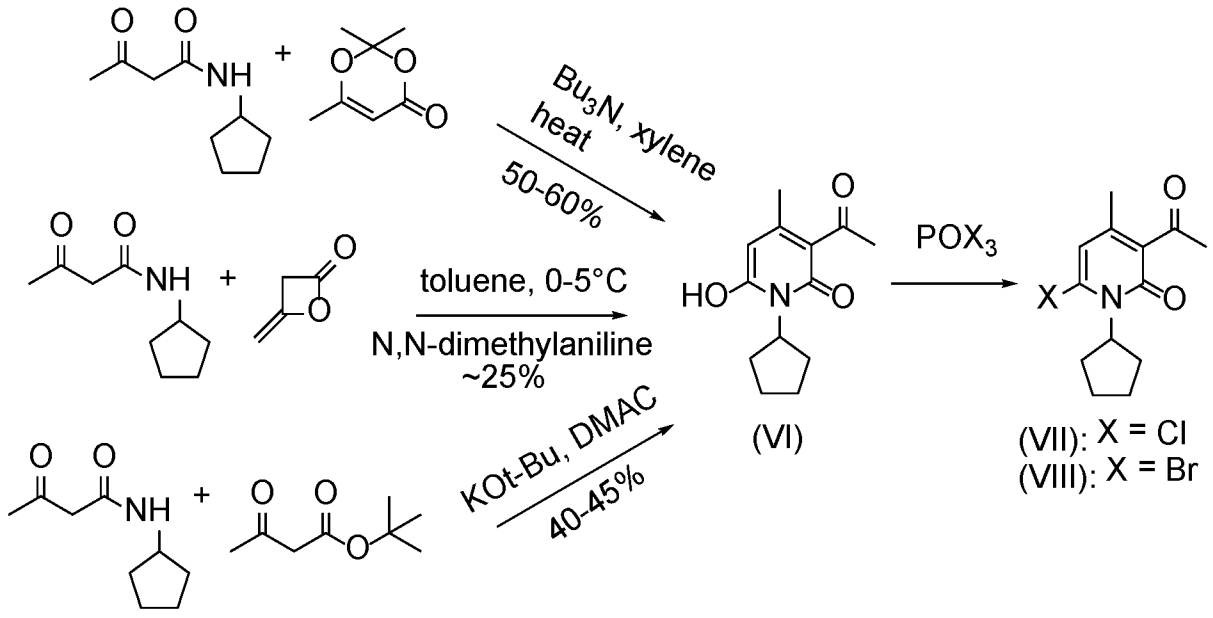
The present invention provides more efficient and convergent routes to prepare palbociclib, involving direct coupling of a suitable 2-halopyridine precursor with an acetyl-substituted pyridone intermediate, e.g., compounds of Formulae (II) or (IV), in which the 6-acetyl or 3-acetyl group, respectively, is already installed. These improved processes avoid the Heck reaction used in the commercial route that indirectly installs the acetyl group. A retrosynthetic analysis of the improved routes is provided in Scheme 2.

Scheme 2



The compounds of Formulae (II) and (IV) were prepared via the intermediacy of the compound of Formula (VI), N-cyclopentyl-3-acetyl-4-methyl-6-hydroxy-2-pyridone, and the corresponding 6-halopyridone compounds of Formulae (VII) and (VIII), which were prepared as shown in Scheme 3.

Scheme 3



Preparation of N-cyclopentyl-3-acetyl-4-methyl-6-hydroxy-2-pyridone (VI) was described in Example 2 of Chinese Patent No. 104478874, but no analytical details were supplied. The reported synthesis required N-acetoacetylation of cyclopentylamine with ethyl acetoacetate to obtain N,N-bis(acetoacetyl)cyclopentylamine, followed by intramolecular condensation in the presence of an alkaline reagent to provide N-cyclopentyl-3-acetyl-4-methyl-6-hydroxy-2-pyridone as an oil. The preparation of N,N-bis(acetoacetyl)cyclopentylamine could not be repeated under the conditions reported, with reaction of acetoacetates with primary or secondary amines likely giving only enamines, which did not react further under the reported conditions.

Preparation of the N-cyclohexyl analog of the compound of Formula (VI) in modest yield has been described by reaction of diketene with N-substituted acetoacetamides, using a weak base (i.e., N,N-dimethylaniline) as catalyst. See Radke, DE2705562, Dimroth and Radke, Liebigs Ann. Chim. (1979), 769. In the absence of base, the isomeric 3-acetyl-4-hydroxy-6-methyl-2-pyridones were isolated as the dominant products.

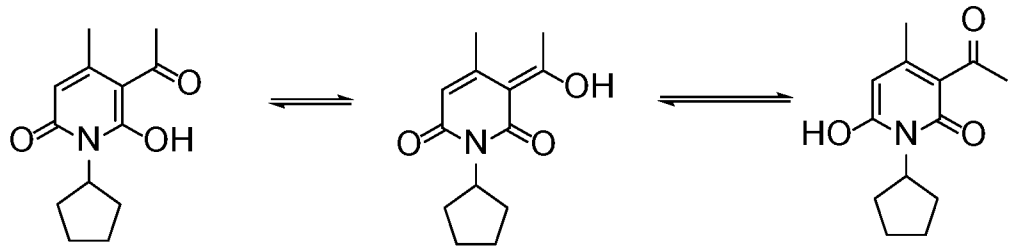
As diketene is no longer available on a laboratory scale due to safety concerns, the diketene adduct with acetone, 2,2,6-trimethyl-1,3-dioxin-4-one, was used to prepare the compound of Formula (VI). Lipophilic trialkylamines, such as tributylamine, were found to be preferred catalysts when 2,2,6-trimethyl-1,3-dioxin-4-one was used as the acetoacetylating agent. These bases were found to suppress the formation of the isomeric pyridones. Efficient methods have also been developed for separation of the compound of Formula (VI) from neutral by-products and from the main by-product, dehydroacetic acid.

Alternatively, the compound of Formula (VI) was prepared by base-catalyzed condensation of tert-butyl acetoacetate (or other alkyl esters) with N-cyclopentylacetoacetamide. The compound of Formula (VI) was also prepared through a one-pot synthesis by reaction of N-cyclopentylacetoacetamide with diketene generated *in situ* from acetyl chloride and triethylamine and distillation (see Nakashige et al., Tetrahedron Letters, (2015), 56:3531-3533; 2015), followed by treatment with a weak base such as N,N-dimethylaniline.

The compound of Formula (VI) was isolated as a highly crystalline solid when prepared by the methods of the current invention. The compound of Formula (VI) was found by single crystal XRD (FIG. 1) to exist in the solid form as a mixture of two tautomeric forms, the 2-hydroxy tautomer (2-OH) (VI-a) and the enol form of the acetyl moiety, (3(Ac)-OH) (VI-b). A third tautomer, having the 6-hydroxy (6-OH) (VI-c), appears

to be predominant in solution based on NMR data. Tautomeric forms are shown in in Scheme 4.

Scheme 4



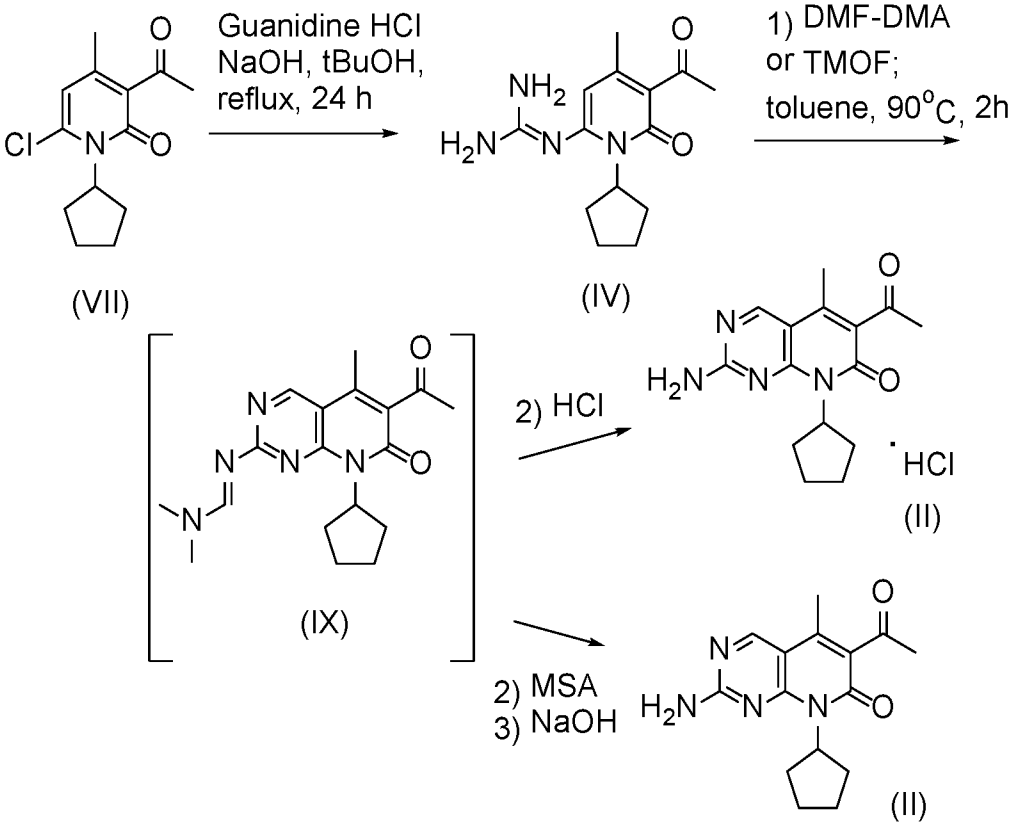
(VI-a) (VI-b) (VI-c)

As shown in Scheme 3, reaction of the compound of Formula (VI) with $POCl_3$ provided the compound of Formula (VII), 3-acetyl-6-chloro-1-cyclopentyl-4-methylpyridin-2(1H)-one, while reaction with $POBr_3$ provided the compound of Formula (VIII), 3-acetyl-6-bromo-1-cyclopentyl-4-methylpyridin-2(1H)-one. The compounds of Formulae (VII) and (VIII) were obtained in good yields and with excellent regioselectivity. Without wishing to be bound by theory, while this regioselectivity was unexpected, it can potentially be explained by the lower reactivity of the two hydrogen-bonded tautomers (VI-a) and (VI-b), and the dominance of non-hydrogen-bonded tautomer (VI-c) in solution, which may be stabilized by hydrogen-bonding to the solvent.

The compounds of Formula (IV) and (II) were prepared as described in Scheme 5. Reaction of the compound of Formula (VII) with guanidine hydrochloride provided the compound of Formula (IV). Other guanylation reagents can be used in this reaction, including guanidine salts, e.g., guanidine hydrochloride, guanidine carbonate salt and guanidine hydrogen carbonate, and N-acyl guanidine derivatives, such as N-formyl guanidine.

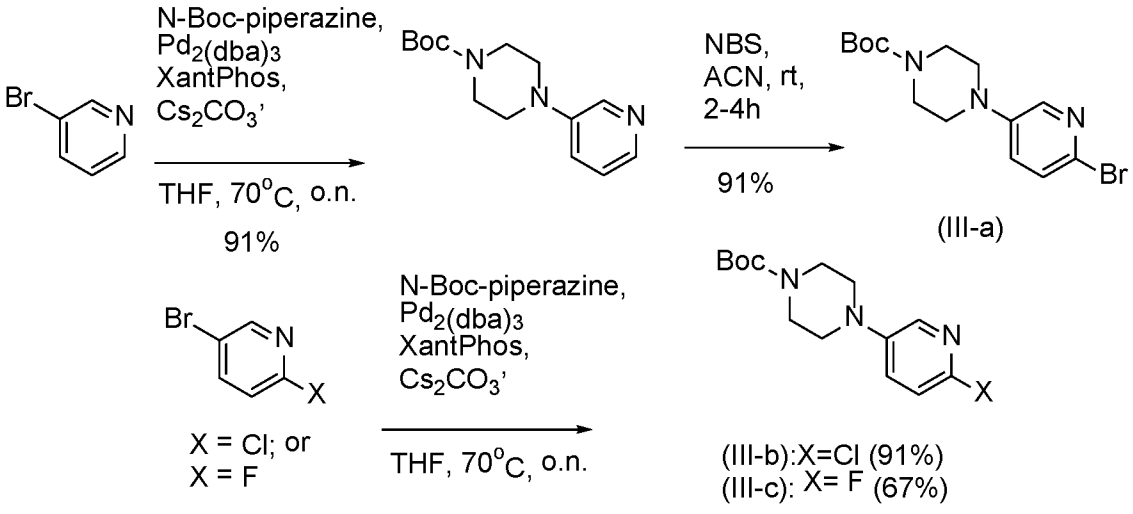
Reaction of the compound of Formula (IV) with the formylation reagent, N,N-dimethyl formamide dimethyl acetal (DMF-DMA), underwent cyclization to provide the amidine intermediate of Formula (IX) in situ. Acidic hydrolysis of the compound of Formula (IX) provided the 2-aminopyrimidine compound of Formula (II) in high yield as the hydrochloride (HCl) salt following workup with aqueous HCl, or as the free base following treatment with methanesulfonic acid (MSA) followed by base (Scheme 5). The compound of Formula (IV) has not been reported previously. The compound of Formula (II) has been described previously (Toogood et al., J. Med. Chem., (2005), 48:2388-2406 and WO 03/062236) via a much less efficient route. Other formylation reagents, such as trimethyl orthoformate (TMOF), can be used in the cyclization reaction to provide the compound of Formula (II).

Scheme 5



As shown in Scheme 6, 2-halo-5-(4-Boc-piperazin-1-yl)-pyridines of Formula (III) were prepared as described in the literature. The compound of Formula (III-a) was prepared according to Audouze et al., J. Med. Chem. (2006), 49:3159-3171. The compound of Formula (III-b) was prepared according to Lu & Schulze-Gahmen, J. Med. Chem. (2014), 57:3430-3449. The compound of Formula (III-c) was prepared according to Wodtke et al., J. Med. Chem. (2018), 61:4528-4560. The compounds of Formulae (III-a), (III-b) and (III-c) are stable crystalline solids and were prepared in 1-2 steps and up to 90% overall yields as shown in Scheme 6.

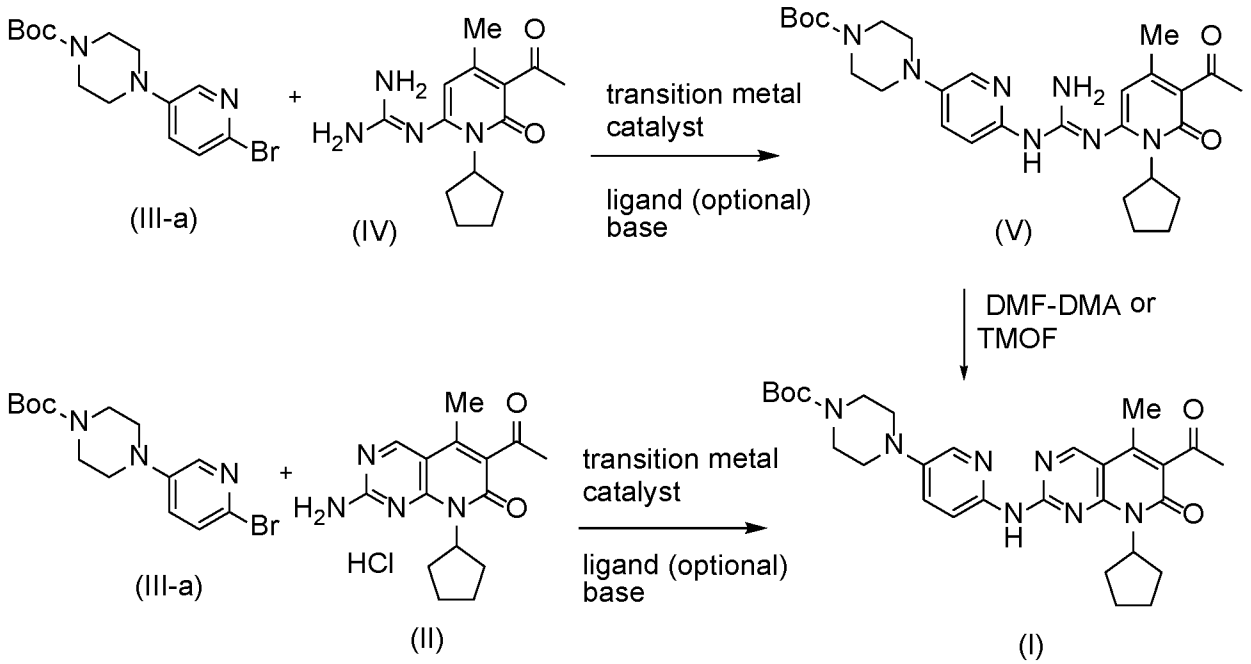
Scheme 6



The compound of Formula (IV) was coupled with bromopyridine compound of Formula (III-a) in the presence of a transition metal catalyst, a base, and optionally a ligand, to give the compound of Formula (V). The compound of Formula (V) was converted to the compound of Formula (I) by reaction with a formylation reagent, e.g., DMF-DMA, and intermolecular cyclization as shown in Scheme 7.

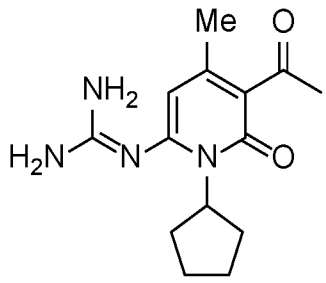
The compound of Formula (II) was coupled with the bromopyridine compound of Formula (III-a) in the presence of a transition metal catalyst, a base, and optionally a ligand, to give the compound of Formulae (I), as shown in Scheme 7.

Scheme 7



Suitable transition metal catalysts for the reactions in Scheme 7 include palladium(0), palladium(II), copper(I) or copper(II) catalysts (i.e., Pd(0), Pd(II), Cu(I) or Cu(II) catalysts).

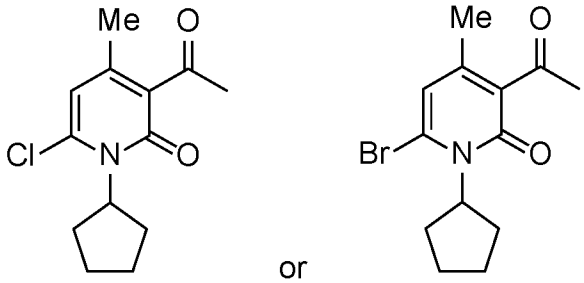
In a first aspect, the invention provides a process for the preparation of the compound of Formula (IV):



(IV), or a salt thereof,

comprising:

(a) reacting a compound of Formula (VII) or (VIII) prepared by the process according to any of the embodiments described herein:



(VII) (VIII)

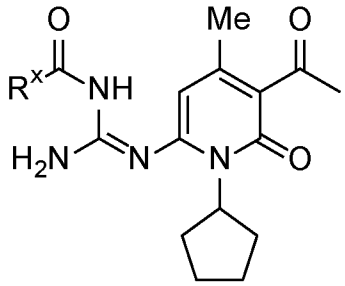
with a guanylation reagent and a base in a suitable solvent, to provide the compound of Formula (IV).

In some embodiments of the first aspect, the process further comprises: (b) isolating the compound of Formula (IV) by extraction into an aqueous acidic solution, adjusting the pH with base to basic pH, and collecting the precipitated compound of Formula (IV) by filtration.

The reactant in step (a) is preferably the compound of Formula (VII). Alternatively, the reactant in step (a) is the compound of Formula (VIII).

Preferably, the guanylation reagent is a guanidine salt selected from the group consisting of guanidine hydrochloride, guanidine carbonate salt and guanidine hydrogen carbonate.

Alternatively, the guanylation reagent in step (a) may be an N-acyl guanidine of formula $R^xC(O)N=C(NH_2)_2$, where R^x is H, C_1-C_4 alkyl, optionally substituted phenyl or optionally substituted benzyl, and step (a) provides an intermediate of Formula (IV^x):



(IV^x)

where R^x is H, C_1-C_4 alkyl, optionally substituted phenyl or optionally substituted benzyl; and the process further comprises:

(b) hydrolyzing the compound of Formula (IV^o) with base;

to provide the compound of Formula (IV).

Optional substituent groups when R^x is optionally substituted phenyl or optionally substituted benzyl are selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy,

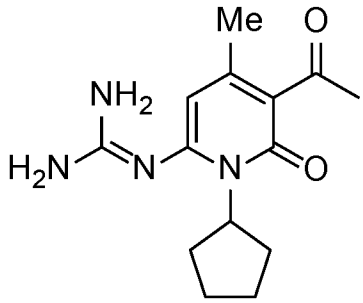
halo, C_1-C_4 haloalkyl, and C_1-C_4 haloalkoxy. In a preferred embodiment, the N-acyl guanidine reagent is N-formyl guanidine (i.e., R^x is H), and the intermediate of Formula (IV^x) is hydrolyzed to provide the compound of Formula (IV).

The base used in preparation of the compound of Formula (IV) in step (a) is preferably an alkali metal hydroxide, alkoxide or carbonate base, or an alkaline earth hydroxide, alkoxide or carbonate base. More preferably, the base is sodium hydroxide, sodium tert-butoxide, sodium tert-pentoxide, potassium hydroxide, potassium tert-butoxide, potassium tert-pentoxide, potassium carbonate or cesium carbonate.

Preferably, the solvent in step (a) of the guanylation reaction comprises a tertiary alcohol. More preferably, the solvent is tert-butanol or tert-amyl alcohol.

Each of the embodiments described herein for the first aspect may be combined with any other embodiment described for the first aspect, provided the embodiments are not inconsistent with each other.

In a further aspect, the invention provides a compound of Formula (IV):

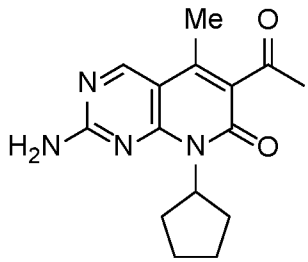


,

(IV)

or a salt thereof.

In a second aspect, the invention provides a process for the preparation of the compound of Formula (II):

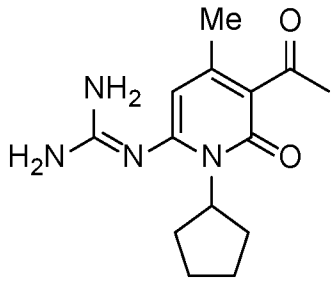


(II)

or a salt thereof,

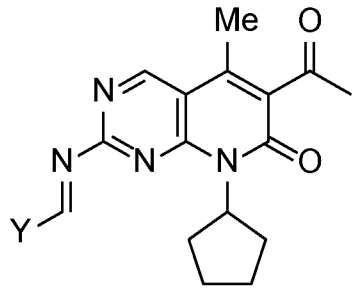
comprising:

(a) reacting a compound of Formula (IV) prepared by the process according to any of the embodiments described herein:



(IV)

with a formylation reagent which is a di(C_1-C_4 alkyl)formamide-di(C_1-C_4 alkyl) acetal or a tri(C_1-C_4 alkyl) orthoformate in a suitable solvent under dehydrative conditions to provide a compound of Formula (X):



(X)

wherein Y is N(C_1-C_4 alkyl)$_2$ or O(C_1-C_4 alkyl);

(b) optionally isolating the compound of Formula (X); and

(c) hydrolysis of the compound of Formula (X) in the presence of an acid in a suitable solvent to provide the compound of Formula (II), or a salt thereof.

The process may further comprise:

(d) isolating the compound of Formula (II) as free base by partitioning the reaction mixture between water and a suitable organic solvent, then treating with base and extracting the free base compound of Formula (II) into the organic solvent; or

(e) isolating the compound of Formula (II) as a salt by filtration of the cooled reaction mixture of step (c); and

(f) optionally providing the compound of Formula (II) as a free base by dissolving the salt isolated in step (e) in a suitable solvent, typically comprising water, neutralizing with a suitable base, and then extracting the free base of Formula (II) with a suitable organic solvent or crystallizing the free base of Formula (II) from a suitable solvent.

Suitable bases include amine bases, such as triethylamine. Suitable solvents for use in the crystallization in step (f) include alcohol solvents.

Preferably, the intermediate of Formula (X) is hydrolyzed without isolation to provide the compound of Formula (II).

In some embodiments, step (b) comprises isolating the compound of Formula (X). For example, the compound of Formula (X) may be isolated by cooling the reaction mixture of step (a), extracting the salt into dilute aqueous acid, and adjusting the pH to basic pH with base and collecting the compound of Formula (X) by filtration.

Preferably, the formylation reagent in step (a) is a formic acid ortho ester or a formamide acetal selected from the group consisting of N,N-dimethyl formamide dimethyl acetal (DMF-DMA) and trimethyl orthoformate (TMOF).

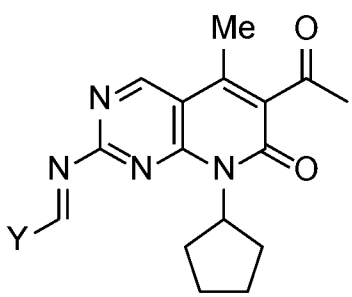
Preferably, the solvent in step (a) is an aromatic hydrocarbon and the dehydrative conditions in step (a) comprise heating the solution comprising the compound of Formula (IV) and the formylation reagent at about 90ºC for about 2 hours.

In some embodiments of the second aspect, the hydrolysis in step (c) comprises reacting the compound of Formula (X) with an organic or inorganic acid in a suitable solvent or solvent mixture, typically comprising water, to provide the compound of Formula (II), or a salt thereof. Preferably, the acid is aqueous hydrochloric acid (HCl). More preferably, the hydrolysis in step (c) comprises heating a solution comprising the compound of Formula (X) and aqueous HCl at about 50ºC for about 2-4 hours. The HCl salt of Formula (II) is quite insoluble and may be isolated by filtration from the aqueous solvent mixture.

The compound of Formula (II) may be conveniently prepared as a free base by use of acids that provide water soluble salts in the hydrolysis in step (c). In particular, sulfuric acid and methanesulfonic acid provided the corresponding salts of Formula (II), simplifying the extractive workup. Neutralization of the acidic reaction mixture comprising such water soluble salts with base and extraction with a suitable organic solvent permits isolation of the compound of Formula (II) as a free base without isolation of the salt formed in step (c).

Each of the embodiments described herein for the second aspect may be combined with any other embodiment described for the second aspect, provided the embodiments are not inconsistent with each other.

In a third aspect, the invention provides a compound of Formula (X):



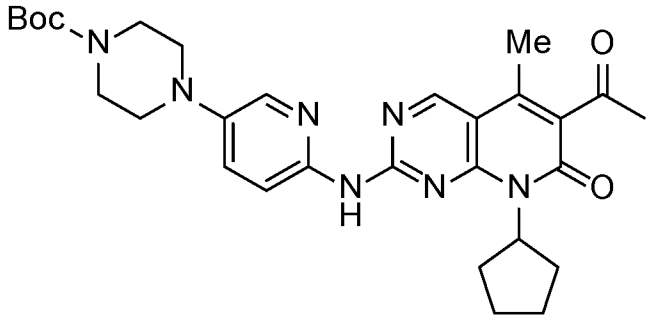
(X)

where Y is $N(C_1\text{-}C_4\ alkyl)_2$ or $O(C_1\text{-}C_4\ alkyl)$.

The compound of Formula (X) may be prepared as described in the second aspect herein, or any of the embodiments or combination of embodiments thereof.

Each of the embodiments described herein for the third aspect may be combined with any other embodiment described for the third aspect, provided the embodiments are not inconsistent with each other.

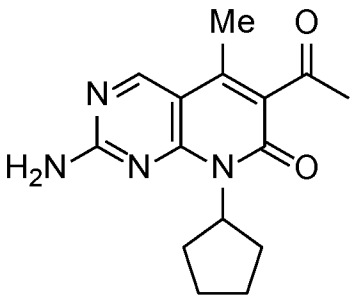
In a fourth aspect, the invention provides a process for the preparation of the compound of Formula (I):



(I)

comprising:

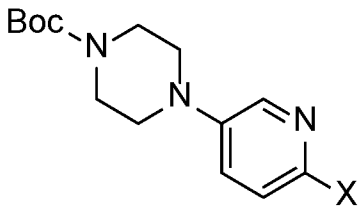
(a) coupling a compound of Formula (II) prepared by the process according to any of the embodiments described herein:



(II)

or a salt thereof,

with a compound of Formula (III):

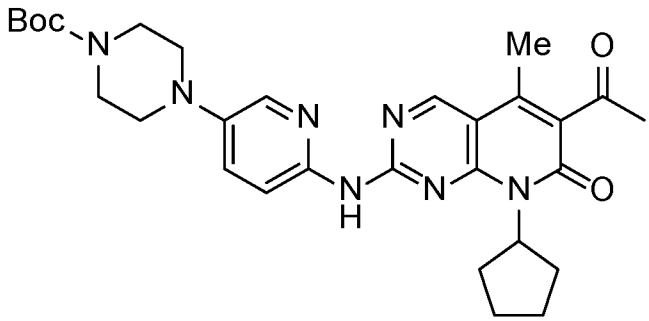


(III)

where X is a leaving group selected from a halo and a sulfonate ester,

in the presence of a transition metal catalyst, a base, and optionally a ligand, in a suitable solvent to provide the compound of Formula (I).

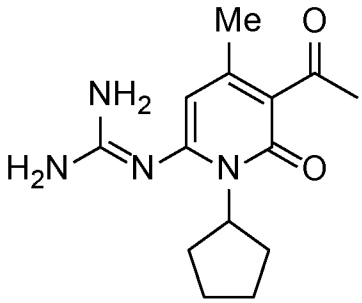
In a fifth aspect, the invention provides another process for the preparation of the compound of Formula (I):



(I)

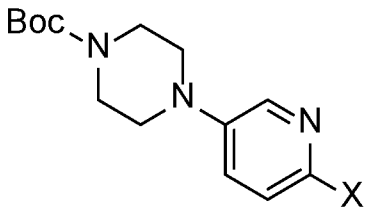
comprising:

(a) coupling a compound of Formula (IV) prepared by the process according to any of the embodiments described herein:



(IV)

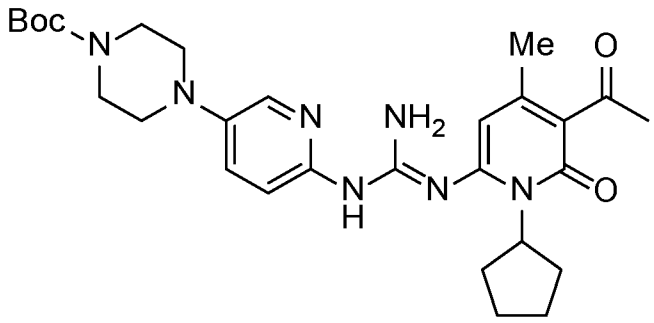
with a compound of Formula (III):



(III)

where X is a leaving group selected from a halo and a sulfonate ester,

in the presence of a transition metal catalyst, a base, and optionally a ligand, in a suitable solvent to provide the compound of Formula (V):



; and

(V)

(b) reacting the compound of Formula (V) with a formylation reagent in a suitable solvent under dehydrative conditions to provide a compound of Formula (I),

wherein the formylation reagent is a di(C_1-C_4 alkyl)formamide di(C_1-C_4 alkyl) acetal or a tri(C_1-C_4 alkyl) orthoformate.

In some embodiments of the fourth and fifth aspects, X is selected from the group consisting of bromo, chloro, iodo, trifluoromethanesulfonate, and tosylate (i.e., Br, Cl, I, OTf, and OTs). Preferably, X is bromo.

Preferably, the transition metal catalyst in the fourth and fifth aspects is a palladium catalyst.

Suitable palladium catalysts include palladium(0) or palladium(II) reagents and complexes. Examples of suitable palladium reagents include palladium(0) bis(dibenzylideneacetone) ($Pd(dba)_2$), tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), palladium(II) chloride ($PdCl_2$), palladium(II) acetate ($Pd(OAc)_2$), allylpalladium(II) chloride dimer ($[AllylPdCl]_2$), palladium on carbon (Pd/C), bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride ($PdCl_2(dppf)_2$), tetraaminepalladium(II) chloride ($Pd(NH_3)_4Cl_2$), palladium(II) nitrate ($Pd(NO_3)_2$), tetrachloropalladic acid (H_2PdCl_4), tetraaminepalladium(II) nitrate ($Pd(NH_3)_4](NO_3)_2$), (1,3-bis(diphenylphosphino)propane)palladium(II) chloride ($PdCl_2(dippp)$), palladium(II) bis(acetylacetonate) ($Pd(acac)_2$), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$).

Preferably, the palladium catalyst is selected from the group consisting of $Pd(dba)_2$, $Pd_2(dba)_3$, $[AllylPdCl]_2$, $PdCl_2$, $Pd(OAc)_2$ and Pd/C. More preferably, the palladium catalyst is a Pd(II) catalyst selected from the group consisting of $[AllylPdCl]_2$, $PdCl_2$, and $Pd(OAc)_2$.

In some embodiments of the fourth and fifth aspect, the process further comprises a ligand.

When the transition metal catalyst is a palladium catalyst, preferably the ligand is a phosphine ligand. Suitable phosphine ligands for use with palladium catalysts include monophosphine or diphosphine ligands. Examples of monophosphine ligand include: Xphos, $P(tBu)_3$, RuPhos, tBuXphos, CyJohnphos, Johnphos, SPhos, tBuBrettphos, Me4tBuXPhos, DavePhos, BrettPhos, Bippyphos, di(1-adamantyl)-n-butylphosphine (CataCXium A), di-t-butylphosphine oxide, $P(o\text{-}tol)_3$, Jackiephos, $P(2\text{-}furyl)_3$, PH_2tBu, PH_2Cy, PH_2Me, 4-(N,N-dimethylamino)phenyl]di-tert-butylphosphine (Amphos), 2-dicyclohexylphosphino-2'-methylbiphenyl, and 2-methyl-2'-dicyclohexyl-phosphino-biphenyl (MebiphPCy2 or MePhos). Examples of biphosphine ligands include: the biphosphine ligand is selected from the group consisting of XantPhos, Binap, dppf, DPEPhos, Josiphos SL-J009-1, dppp, DMPM, 1,2-bis(dicyclohexylphosphino)ethane, dppe, tris(2,4-di-tert-butylphenyl) phosphite monophoshine, and tBuXanthphos. More preferably, the phosphine ligand is selected from the group consisting of $Me_4tBuXPhos$, tBuBrettphos, tBuXphos, Xantphos, Bippyphos, Johnphos, Josiphos SL-J009-1, DPEphos and 1,1'-bis(diphenylphosphino)ferrocene (dppf).

In other embodiments of the fourth and fifth aspects, the transition metal catalyst is a copper catalyst. Suitable copper catalysts include copper(I) or copper(II) reagents and complexes. Examples of suitable copper reagents include copper(I) iodide (CuI), copper(I) trifluoromethanesulfonate (CuOTf), copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$), tetrakis(acetonitrile)copper(I)tetrafluoroborate ($Cu(BF_4)(MeCN)_4$) or tetrakis(acetonitrile) copper(I) hexafluorophosphate ($Cu(PF_6)(MeCN)_4$). In preferred embodiments, the copper catalyst is copper(I) iodide (CuI).

In some embodiments, when the transition metal catalyst is a copper catalyst, the process further comprises a ligand, including, e.g., a diamine, phenanthroline, dipyridyl or phenolic ligand. Suitable ligands include N,N'-dimethylethylenediamine, trans-N,N'-dimethylcyclohexane-1,2-diamine, N,N,N',N'-tetramethylethylenediamine, 8-hydroxy-quinoline, 8-hydroxyquinoline N-oxide, 4,7-diphenyl-1,10-phenanthroline (bathophenanthroline), 4-4′ -dimethoxy-2-2′ -bipyridine, 2,6-dimethylanilino(oxo)acetic acid (DMPAO), 4,4'-di-tert-butyl-2,2'-dipyridyl (Bbbpy), 4,7-dimethoxy-1,10-phenanthroline, 2,2':6',2''-terpyridine, N,N-diethylsalicylamide, 8-acetyl-5,6,7,8-tetrahydroquinoline, picolinic acid N-oxide, L-proline, N,N-dimethylglycine, 2-isobutyrylcyclohexanone, 1,3-di(2-pyridyl)-1,3-propanedione, 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 1,10-phenanthroline, and N-(2,6-dimethylphenyl)-6-hydroxypicolinamide.

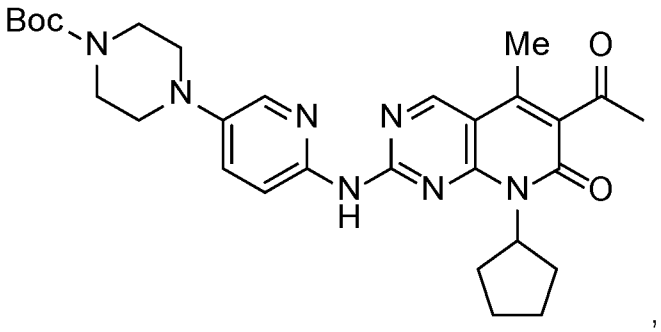
When the transition metal catalyst is a copper catalyst, preferably the ligand is is selected from the group consisting of trans-N,N′-dimethylcyclohexane-1,2-diamine, bathophenanthroline, *N*-(2,6-dimethylphenyl)-6-hydroxypicolinamide, and 8-hydroxy-quinoline N-oxide.

In some embodiments of the fourth and fifth aspects, the base is an alkaline earth carbonate, alkoxide or phosphate base. Preferably, the base is potassium carbonate, cesium carbonate, sodium tert-butoxide, potassium tert-butoxide, or potassium phosphate.

In the fourth and fifth aspects, preferably the solvent comprises tetrahydrofuran, cyclopentyl methyl ether (CPME), methyl tert-butyl ether (MTBE), toluene, xylene, DMF, DMSO or dioxane. Suitable solvents for use with palladium catalysts include non-polar solvents, e.g., toluene or xylene, and alcohol solvents. Suitable solvents for use with copper catalysts include polar aprotic solvents or ethereal solvents, e.g., DMF, DMSO, or dioxane.

Each of the embodiments described herein for the fourth and fifth aspects may be combined with any other embodiment described for the fourth and fifth aspects, provided the embodiments are not inconsistent with each other.

In a sixth aspect, the invention provides a compound of Formula (I):

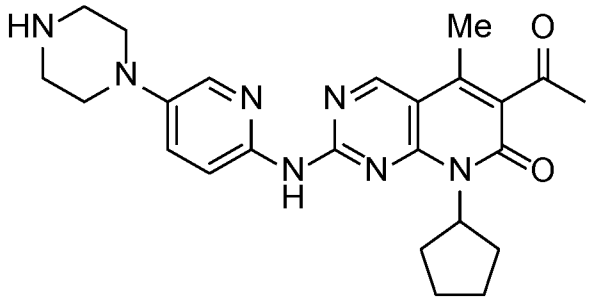


(I)

prepared by the process described in the fourth or fifth aspects, or any of the embodiments or combinations of embodiments thereof.

Each of the embodiments described herein for the sixth aspect may be combined with any other embodiment described for the sixth aspect, provided the embodiments are not inconsistent with each other.

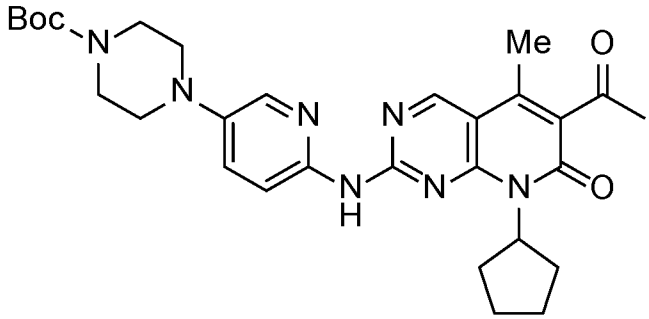
In a seventh aspect, the invention provides a process for the preparation of palbociclib:



or a salt thereof,

comprising:

(a) reacting the compound of Formula (I), prepared by the process according to any of the embodiments described herein:



(I)

with an organic or inorganic acid in a suitable solvent to provide a palbociclib salt; and

(b) isolating the palbociclib salt; or

(c) isolating the palbociclib salt and neutralizing the isolated palbociclib salt to provide the free base of palbociclib; or

(d) neutralizing the palbociclib salt *in situ* to provide the free base of palbociclib.

In some embodiments of the seventh aspect, the process further comprises: (e) crystallizing the free base of palbociclib from a suitable solvent to provide the crystalline free base of palbociclib (Form A), where Form A is as described in International Publication No. WO 2014/128588. Preferably, the crystallization solvent in step (e) is a mixture of anisole and n-butanol. The crystalline free base of palbociclib (Form A) is characterized as having:

(1) a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of: (a) 8.0 ± 0.2, 10.1 ± 0.2 and 11.5 ± 0.2 2θ; or (b) 8.0 ± 0.2, 10.1 ± 0.2, 10.3 ± 0.2, and 11.5 ± 0.2 2θ;

(2) a ^{13}C solid state NMR spectrum comprising resonance (ppm) values of: (a) 12.5 ppm ± 0.2 ppm; (b) 12.5 ppm and 112.4 ppm ± 0.2 ppm; or (c) 12.5 ppm, 112.4 ppm and 143.2 ppm ± 0.2 ppm;

(3) a primary particle size distribution characterized by a D90 value of from about 30 μm to about 65 μm; or

(4) a D[4,3] value of from about 15 μm to about 30 μm;

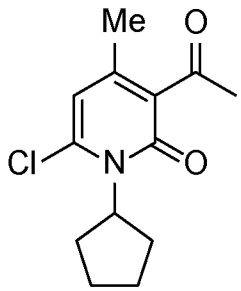
or any combination of two or more of (1)(a), (1)(b), (2)(a), (2)(b), (2)(c), (3), or (4).

In an eighth aspect, the invention provides palbociclib, or a salt thereof, prepared by the process of the seventh aspect, or any of the embodiments or combinations of embodiments thereof.

In a ninth aspect, the invention provides crystalline free base of palbociclib (Form A), prepared by the process of the seventh aspect, wherein the process further comprises step (e) as described.

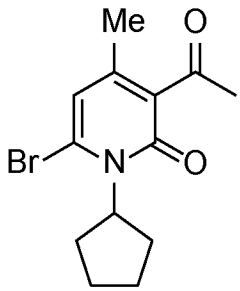
Each of the embodiments described herein for the seventh, eighth or ninth aspects may be combined with any other embodiment described for the seventh, eighth or ninth aspects, provided the embodiments are not inconsistent with each other.

In a tenth aspect, the invention provides a process for the preparation of a compound of Formulae (VII) or (VIII):



(VII)

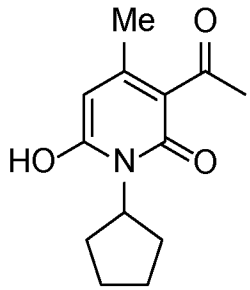
or



(VIII)

comprising:

(a) reacting a compound of Formula (VI), or a tautomer thereof prepared by the process according to any of the embodiments described herein:



(VI)

with a halogenating agent, and optionally a suitable solvent,

to provide the compound of Formula (VII) or (VIII).

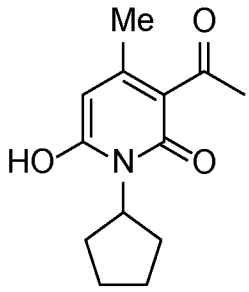
In some embodiments of the tenth aspect, the process further comprises: (b) isolating the compound of Formula (VII) or (VIII) by adding water to destroy excess halogenating agent, adjusting the pH with base to neutral, extracting with an organic solvent and concentrating the organic solvent layer to provide the compound of Formula (VII) or (VIII).

In preferred embodiments of the tenth aspect, the halopyridone is the compound of Formula (VII), and the halogenating agent is $POCl_3$. In other embodiments of the tenth aspect, the halopyridone is the compound of Formula (VIII), and the halogenating agent is $POBr_3$.

In some embodiments of the tenth aspect, the halogenation process includes a solvent, where the solvent comprises a halogenated solvent, an aromatic hydrocarbon solvent, a dipolar aprotic solvent, or an ethereal solvent. In preferred embodiments, the solvent comprises dichloromethane, toluene, chlorobenzene, acetonitrile, tetrahydrofuran, CPME or MTBE

Each of the embodiments described herein for the tenth aspects may be combined with any other embodiment described for the tenth aspect, provided the embodiments are not inconsistent with each other.

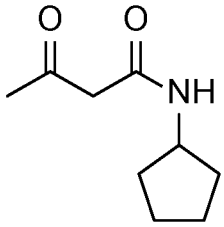
In an eleventh aspect, the invention provides a process for the preparation of a compound of Formula (VI), or a tautomer thereof:



(VI)

comprising:

(a) reacting N-cyclopentylacetoacetamide (CPA) of Formula (XI):



(XI)

with an acetoacetylating reagent and a base in a suitable solvent to provide the compound of Formula (VI).

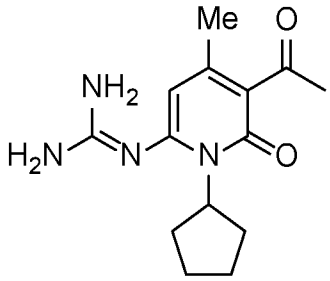
In some embodiments of the eleventh aspect, the process further comprises: (b) isolating the compound of Formula (VI) by extraction into an aqueous basic solution, adjusting the pH with acid to neutral/acidic pH, and collecting the precipitated compound of Formula (VI) by filtration; and optionally (c) recrystallizing the compound of Formula (VI) from a suitable solvent. Suitable solvents include alcohols and polar aprotic solvents, such as MeOH or acetonitrile.

In preferred embodiments of the eleventh aspect, the acetoacetylating reagent is 2,2,6-trimethyl-1,3-dioxin-4-one, tert-butyl acetoacetate or diketene.

In some embodiments of the eleventh aspect, the base is a trialkylamine base. In some embodiments of the eleventh aspect, the base is an alkali metal or alkaline earth alkoxide base. In some embodiments of the eleventh aspect, the base is N,N-dimethylaniline.

Described below are preferred embodiments of the invention, E1 to E57:

E1. A process for the preparation of the compound of Formula (IV):

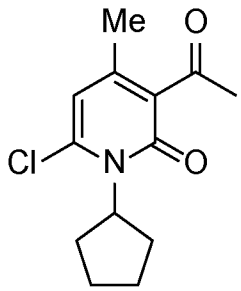


,

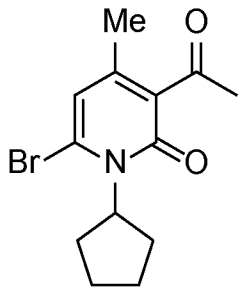
(IV)

comprising:

(a) reacting a compound of Formula (VII) or (VIII):



or



(VII) (VIII)

with a guanylation reagent and a base in a suitable solvent;

to provide the compound of Formula (IV).

E2. The process of embodiment E1, further comprising: (b) isolating the compound of Formula (IV) by extraction into an aqueous acidic solution, adjusting the pH with base to basic pH, and collecting the precipitated compound of Formula (IV) by filtration.

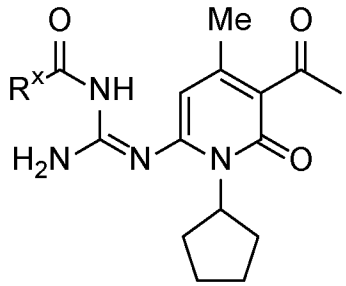
E3. The process of embodiment E1 or E2, wherein the reactant in step (a) is the compound of Formula (VII).

E4. The process of embodiment E1 or E2, wherein the reactant in step (a) is the compound of Formula (VIII).

E5. The process of any one of embodiments E1 to E4, wherein the guanylation reagent is a guanidine salt or an N-acyl guanidine.

E6. The process of embodiment E5, wherein the guanylation reagent is a guanidine salt selected from the group consisting of guanidine hydrochloride, guanidine carbonate salt and guanidine hydrogen carbonate.

E7. The process of embodiment E5, wherein the guanylation reagent in step (a) is an N-acyl guanidine of formula $R^xC(O)N=C(NH_2)_2$, where R^x is H, C_1-C_4 alkyl, optionally substituted phenyl or optionally substituted benzyl, and step (a) provides an intermediate of Formula (IV^x):



(IV^x)

where R^x is H, C_1-C_4 alkyl, optionally substituted phenyl or optionally substituted benzyl; and the process further comprises:

(b) hydrolyzing the compound of Formula (IV^x) with base;

to provide the compound of Formula (IV).

E8. The process of embodiment E7, wherein the guanylation reagent is N-formyl guanidine.

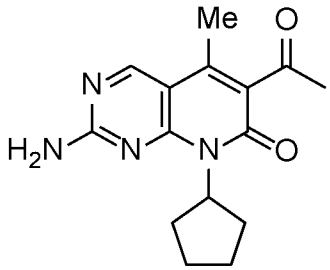
E9. The process of any one of embodiments E1 to E8, wherein the base is an alkali metal hydroxide, alkoxide or carbonate base, or an alkaline earth hydroxide, alkoxide or carbonate base.

E10. The process of embodiment E9, wherein the base is sodium hydroxide, sodium tert-butoxide, sodium tert-pentoxide, potassium hydroxide, potassium tert-butoxide, potassium tert-pentoxide, potassium carbonate or cesium carbonate.

E11. The process of any one of embodiments E1 to E10, wherein the solvent comprises a tertiary alcohol.

E12. The process of embodiment E11, wherein the solvent is tert-butanol or tert-amyl alcohol.

E13. A process for the preparation of the compound of Formula (II):

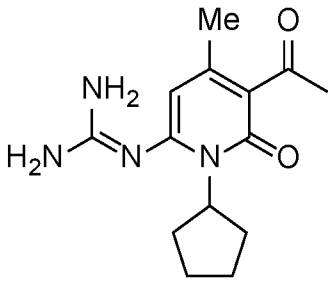


(II)

or a salt thereof,

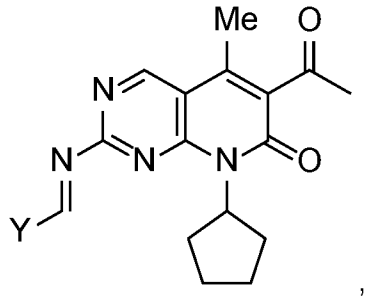
comprising:

(a) reacting a compound of Formula (IV) prepared by the process according to any one of embodiments E1 to E12:



(IV)

with a formylation reagent which is a di(C_1-C_4 alkyl)formamide di(C_1-C_4 alkyl) acetal or a tri(C_1-C_4 alkyl) orthoformate in a suitable solvent under dehydrative conditions to provide a compound of Formula (X):



(X),

wherein Y is N(C_1-C_4 alkyl)$_2$ or O(C_1-C_4 alkyl);

(b) optionally isolating the compound of Formula (X); and

(c) hydrolysis of the compound of Formula (X) in the presence of an acid in a suitable solvent to provide the compound of Formula (II), or a salt thereof.

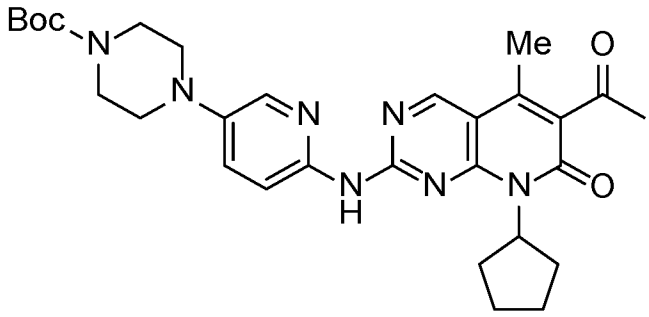
E14. The process of embodiment E13, wherein the formylation reagent in step (a) is a formic acid ortho ester or a formamide acetal selected from N,N-dimethyl formamide dimethyl acetal (DMF-DMA)] and trimethyl orthoformate (TMOF).

E15. The process of embodiment E13 or E14, wherein the solvent in step (a) is an aromatic hydrocarbon and the dehydrative conditions in step (a) comprise heating the solution comprising the compound of Formula (IV) and the formylation reagent at about 90ºC for about 2 hours.

E16. The process of any one of embodiments E13 to E15, wherein the acid in step (c) is an organic or inorganic acid.

E17. The process of embodiment E16, wherein the acid in step (c) is aqueous hydrochloric acid (HCl) and the hydrolysis in step (c) comprises heating a solution comprising the compound of Formula (X) and HCl at about 50ºC for about 2-4 hours.

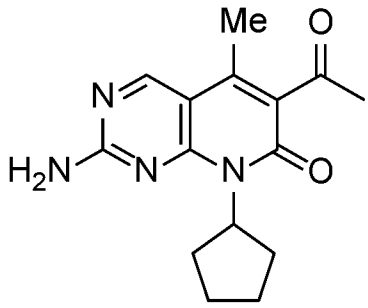
E18. A process for the preparation of the compound of Formula (I):



(I) ,

comprising:

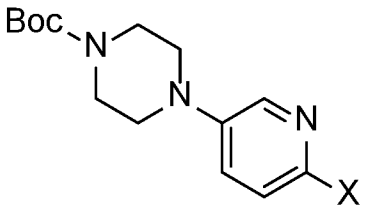
(a) coupling a compound of Formula (II) prepared by the process according to any one of embodiments E13 to E17:



(II)

or a salt thereof,

with a compound of Formula (III):

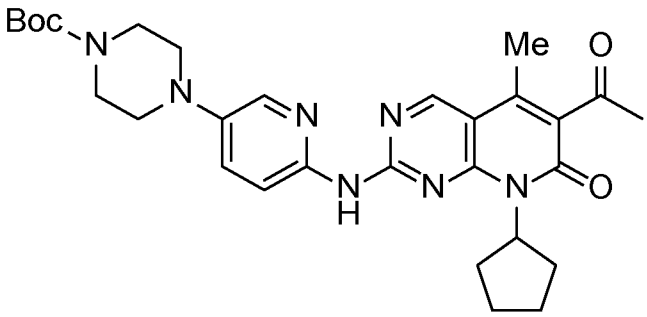


(III)

where X is a leaving group selected from a halo and a sulfonate ester,

in the presence of a transition metal catalyst, a base, and optionally a ligand, in a suitable solvent to provide the compound of Formula (I).

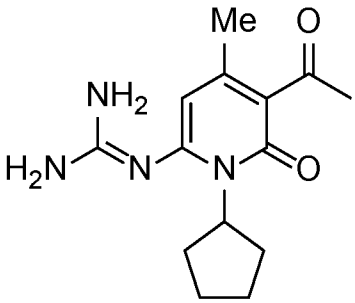
E19. A process for the preparation of the compound of Formula (I):



(I)

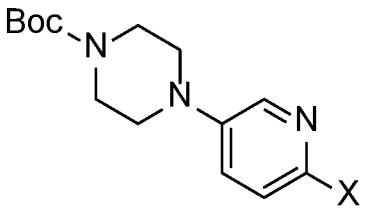
comprising:

(a) coupling a compound of Formula (IV) prepared by the process according to any one of embodiments E1 to E12:



(IV)

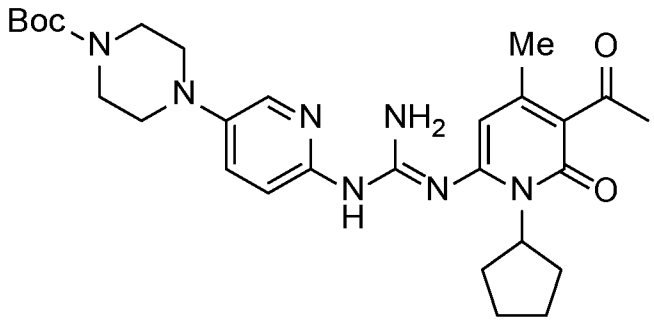
with a compound of Formula (III):



(III)

where X is a leaving group selected from a halo and a sulfonate ester,

in the presence of a transition metal catalyst, a base, and optionally a ligand, in a suitable solvent to provide the compound of Formula (V):



; and

(V)

(b) reacting the compound of Formula (V) with a formylation reagent in a suitable solvent under dehydrative conditions to provide a compound of Formula (I),

wherein the formylation reagent is a di(C_1-C_4 alkyl)formamide di(C_1-C_4 alkyl) acetal or a tri(C_1-C_4 alkyl) orthoformate.

E20. The process of embodiment E18 or E19, wherein X is Br.

E21. The process of any one of embodiments E18 to E20, wherein the transition metal catalyst is a palladium catalyst.

E22. The process of embodiment E21, wherein the palladium catalyst is selected from the group consisting of $Pd(dba)_2$, $Pd_2(dba)_3$, $PdCl_2$, $Pd(OAc)_2$, $[AllylPdCl]_2$, and Pd/C.

E23. The process of embodiment E21 or E22, wherein step (a) further comprises a ligand.

E24. The process of embodiment E23, wherein the ligand is a phosphine ligand selected from the group consisting of Me_4tBuXPhos, tBuBrettphos and tBuXphos, Xantphos, Bippyphos, Johnphos, Josiphos SL-J009-1, DPEphos and 1,1'-bis(diphenyl-phosphino)ferrocene (dppf).

E25. The process of any one of embodiments E18 to E20, wherein the transition metal catalyst is a copper catalyst.

E26. The process of embodiment E25, wherein the copper catalyst is copper(I) iodide (CuI).

E27. The process of embodiment E25 or E26, wherein step (a) further comprises a ligand.

E28. The process of embodiment E27, wherein the ligand is a diamine, phenanthroline, dipyridyl or phenolic ligand.

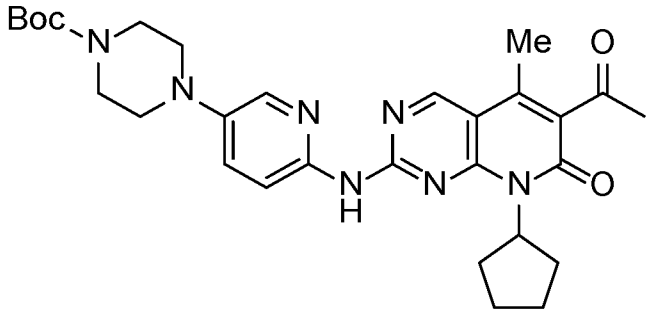
E29. The process of embodiment E28, wherein the ligand is trans-N,N′-dimethylcyclohexane-1,2-diamine, bathophenanthroline, *N*-(2,6-dimethylphenyl)-6-hydroxypicolinamide, or 8-hydroxyquinoline N-oxide.

E30. The process of any one of embodiments E18 to E29, wherein the base in step (a) is an alkali metal carbonate, alkali metal alkoxide, alkali metal phosphate, alkaline earth carbonate, alkaline earth alkoxide or alkaline earth phosphate base.

E31. The process of embodiment E30, wherein the base in step (a) is potassium carbonate, cesium carbonate, sodium tert-butoxide, potassium tert-butoxide, or potassium phosphate.

E32. The process of any one of embodiments E18 to E31, wherein the solvent in step (a) comprises tetrahydrofuran, cyclopentyl methyl ether (CPME), methyl tert-butyl ether (MTBE), toluene, xylene, DMF, DMSO or dioxane.

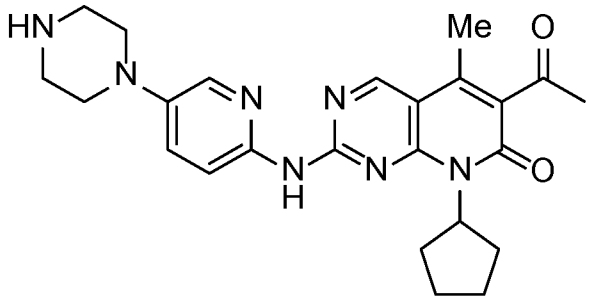
E33. The compound of Formula (I):



(I)

prepared by the process according to any one of embodiments E18 to E32.

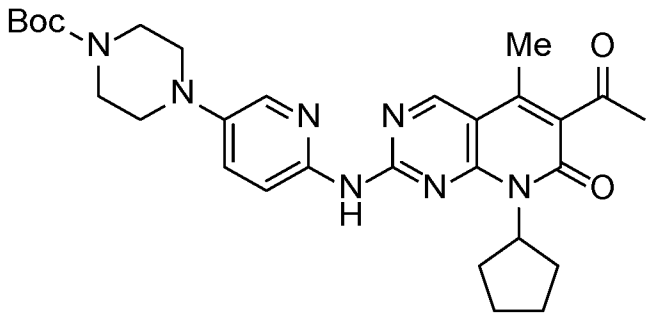
E34. A process for the preparation of palbociclib:



or a salt thereof,

comprising:

(a) reacting the compound of Formula (I), prepared by the process according to any one of embodiments E18 to E32:



(I)

with an organic or inorganic acid in a suitable solvent to provide a palbociclib salt; and

(b) isolating the palbociclib salt; or

(c) isolating the palbociclib salt and neutralizing the isolated palbociclib salt to provide the free base of palbociclib; or

(d) neutralizing the palbociclib salt *in situ* to provide the free base of palbociclib.

E35. The process of embodiment E34, further comprising: (e) crystallizing the free base of palbociclib from a suitable solvent to provide the crystalline palbociclib free base (Form A), having:

(1) a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of: (a) 8.0 ± 0.2, 10.1 ± 0.2 and 11.5 ± 0.2 2θ; or (b) 8.0 ± 0.2, 10.1 ± 0.2, 10.3 ± 0.2, and 11.5 ± 0.2 2θ;

(2) a ^{13}C solid state NMR spectrum comprising resonance (ppm) values of: (a) 12.5 ppm ± 0.2 ppm; (b) 12.5 ppm and 112.4 ppm ± 0.2 ppm; or (c) 12.5 ppm, 112.4 ppm and 143.2 ppm ± 0.2 ppm;

(3) a primary particle size distribution characterized by a D90 value of from about 30 μm to about 65 μm; or

(4) a D[4,3] value of from about 15 μm to about 30 μm;

or any combination of two or more of (1)(a), (1)(b), (2)(a), (2)(b), (2)(c), (3), or (4).

E36. The process of embodiment E35, wherein the crystallization solvent in step (e) is a mixture of anisole and n-butanol.

E37. Palbociclib, or a salt thereof, prepared by the process of embodiment E35 or E36.

E38. Crystalline palbociclib free base (Form A), prepared by the process of embodiment E36 or E37, having:

(1) a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of: (a) 8.0 ± 0.2, 10.1 ± 0.2 and 11.5 ± 0.2 2θ; or (b) 8.0 ± 0.2, 10.1 ± 0.2, 10.3 ± 0.2, and 11.5 ± 0.2 2θ;

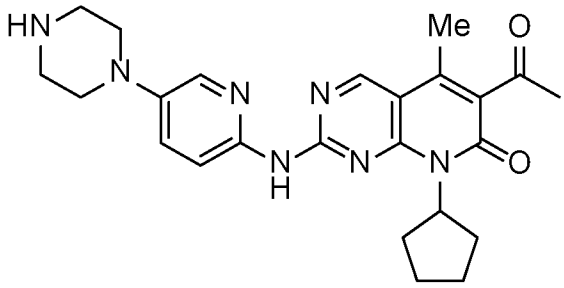
(2) a ^{13}C solid state NMR spectrum comprising resonance (ppm) values of: (a) 12.5 ppm ± 0.2 ppm; (b) 12.5 ppm and 112.4 ppm ± 0.2 ppm; or (c) 12.5 ppm, 112.4 ppm and 143.2 ppm ± 0.2 ppm;

(3) a primary particle size distribution characterized by a D90 value of from about 30 μm to about 65 μm; or

(4) a D[4,3] value of from about 15 μm to about 30 μm;

or any combination of two or more of (1)(a), (1)(b), (2)(a), (2)(b), (2)(c), (3), or (4).

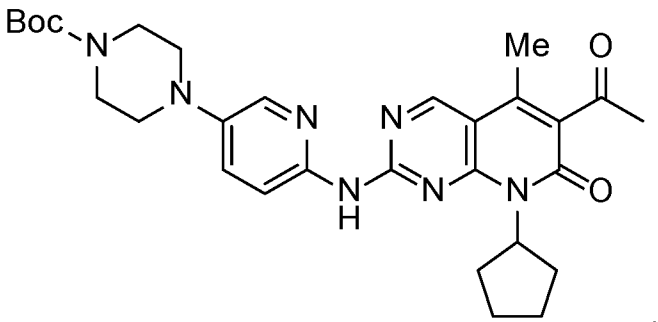
E39. A process for the preparation of palbociclib:



,

comprising:

(a) reacting the compound of Formula (I) prepared by the process according to any one of embodiments E18 to E32:



,

(I)

with formic acid; and

(b) diluting the reaction mixture with water, washing the aqueous layer with one or more organic solvents, and then adjusting the pH of the aqueous phase to basic pH with base to provide palbociclib (free base).

E40. The process of embodiment E39, wherein the process further comprises: (c) cooling the mixture in step (b) to provide a slurry and filtering to isolate palbociclib.

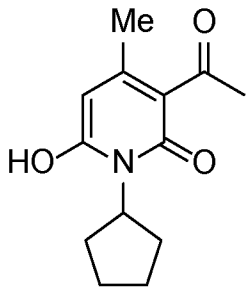
E41. The process of embodiment E39 or E40, wherein the mixture of formic acid and the compound of Formula (I) in step (a) is heated to about 40°C under nitrogen atmosphere until completion of reaction.

E42. The process of any one of embodiments E39 to E41, wherein step (b) comprises washing the aqueous phase with one or more suitable organic solvents (such as CH_2Cl_2, EtOAc, *i*-PrOAc or Anisole) at elevated temperature (preferably about 50-65°C), and adjusting the pH of the aqueous layer to about pH 12.5 with aqueous base (preferably aq. sodium hydroxide) at elevated temperature, preferably about 40°C.

E43. The process of any one of embodiments E39 to E42, wherein the process further comprises: (c) isolating palbociclib by gradually cooling the resulting slurry in step (b) to

about 15°C and then filtering and washing the solid material with water; and optionally (d) drying the solid material under vacuum at about 25°C to obtain palbociclib.

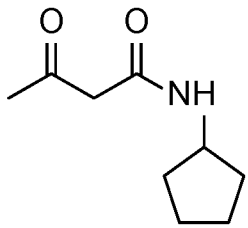
E44. A process for the preparation of a compound of Formula (VI), or a tautomeric form thereof:



(VI)

comprising:

(a) reacting N-cyclopentylacetoacetamide of Formula (XI):



(XI)

with an acetoacetylating reagent and a base in a suitable solvent to provide the compound of Formula (VI).

E45. The process of embodiment E44, wherein the acetoacetylating reagent is 2,2,6-trimethyl-1,3-dioxin-4-one.

E46. The process of embodiment E45, wherein the base is a trialkylamine.

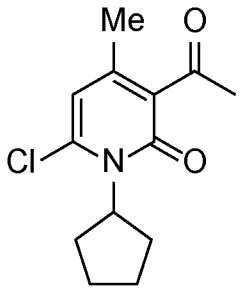
E47. The process of embodiment E44, wherein the acetoacetylating reagent is tert-butyl acetoacetate.

E48. The process of embodiment E47, wherein the base is an alkali metal or alkaline earth alkoxide base.

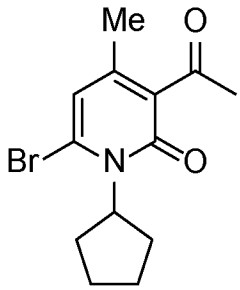
E49. The process of embodiment E44, wherein the acetoacetylating reagent is diketene.

E50. The process of embodiment E49, wherein the base is N,N-dimethylaniline.

E51. A process for the preparation of a compound of Formula (VII) or (VIII):



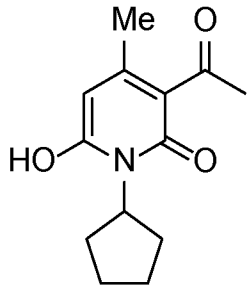
or



(VII) (VIII)

comprising:

(a) reacting a compound of Formula (VI), or a tautomer thereof, prepared by the process of any one of embodiment E44 to E50:



with a halogenating agent, and optionally a suitable solvent,

to provide the compound of Formula (VII) or Formula (VIII).

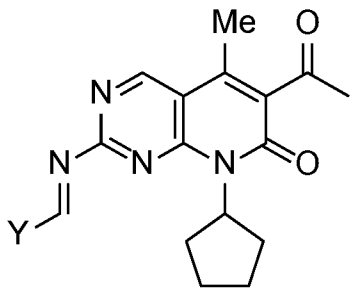
E52. The process of embodiment E51, wherein the reactant is the compound of Formula (VII).

E53. The process of embodiment E51, wherein the reactant is the compound of Formula (VIII).

E54. The process of any one of embodiments E51 to E53, wherein the solvent comprises a halogenated solvent, an aromatic hydrocarbon solvent, a dipolar aprotic solvent, or an ethereal solvent.

E55. The process of embodiment E44, wherein the solvent comprises dichloromethane, toluene, chlorobenzene, acetonitrile, tetrahydrofuran, CPME or MTBE.

E56. A compound of Formula (X):

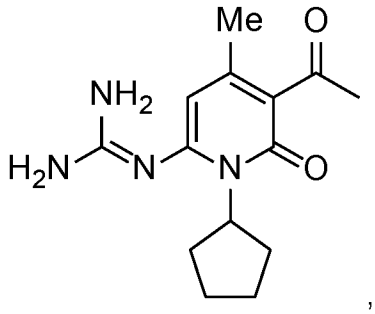


,

(X)

where Y is $N(C_1\text{-}C_4\ alkyl)_2$ or $O(C_1\text{-}C_4\ alkyl)$.

E57. In a further aspect, the invention provides a compound of Formula (IV):



(IV)

or a salt thereof.

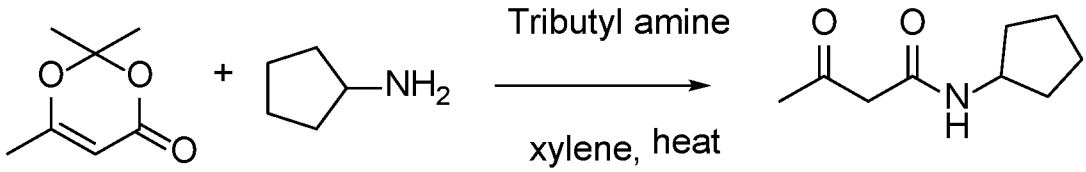
Each of the embodiments described herein for the eleventh aspect may be combined with any other embodiment described for the eleventh aspect, provided the embodiments are not inconsistent with each other.

EXAMPLES

Example 1

Preparation of 3-Acetyl-1-cyclopentyl-6-hydroxy-4-methylpuridin-2(1H)-one (Formula VI)

Step 1: Preparation of N-Cyclopentyl-3-oxobutanamide (Formula XI)



(XI)

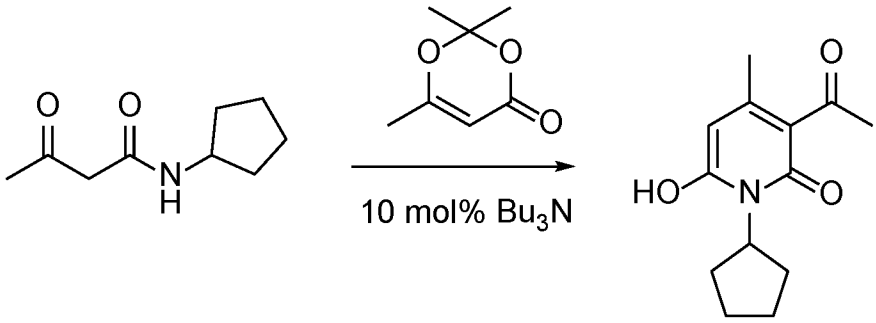
Step No.	Raw material	Quantity	Mol. Wt.	Moles	Mole Ratio	Volumes
1	Cyclopentylamine	230 g	85.15	2.7011	1	-
2	2,2,6-trimethyl-4H-1,3-dioxin-4-one	399.3 g	142.15	2.8091	1.04	-
3	Xylene	1080 mL	-	-	-	4.7
4	Tributylamine	50 g	185.35	0.2701	0.1	-
5	Dichloromethane (DCM)	6.4 L	-	-	-	28

6	Demineralized (DM) water	7.6 L	-	-	-	33

A 5L 4 neck round bottom (RB) flask was charged with cyclopentylamine (230 g, 2.7011 moles) at 25-30°C. The RB flask was charged with xylene (1080 mL). Tributylamine (50 g, 0.2701mole) was added to the RB flask at 25-30°C. The flask was charged with 2,2,6-trimethyl-1,3-dioxin-4-one (399.3 g, 2.8091 mole) and the reaction mixture heated to 110°C for 20-30 min. The reaction mass was stirred at 105-110°C with a gentle reflux for 300-330 min. The reaction mass was cooled to 25-30°C for 20-30 min. The flask was charged with DM water (1085 mL) at 25-30°C and the reaction stirred for 15 min. The layers were allowed to settle for 10 minutes and separated. The xylene layer was extracted with DM water (5 x 1085 mL) and the layers were separated. The xylene layer was extracted with additional DM water (2 x 550 mL) and the layers were separated. The combined aqueous layer was filtered to remove junk material.

A 10-liter RB flask was charged with the clear filtrate, followed by DCM (800 mL) at 25-30°C and the reaction mass was stirred for 15 min. The reaction was allowed to settle for 10 min and the layers were separated at 25-30°C. The aqueous layer was extracted with DCM (7 x 800 mL) and the layers were separated. The DCM layer was distilled at 25-30°C under reduced pressure. The thick mass was dried to a constant weight on a rotary evaporator until a constant weight was achieved. The product was stored at 2-8°C. Dry weight of Ketoamide: 394 g, Yield: 86.2%

Step 2 Preparation of the compound of Formula (VI)



(XI) (VI)

Step No.	Raw material	Quantity	Mol. Wt.	Moles	Mole Ratio	Volumes
1	N-cyclopentyl-3-oxo-butanamide	33.8 g	169.22	0.2	1	-

2	2,2,6-trimethyl-4H-1,3-dioxin-4-one	71 g	142.15	0.5	2.5	-
3	Xylene	656 mL	-	-	-	19.4
4	Tributylamine	3.7 g	185.35	0.02	0.1	-
5	Potassium Carbonate	30.4 g	138.21	0.22	1.1	-
6	Hydrochloric acid	45 mL	-	-	-	-
7	Methanol	206 mL	-	-	-	6.5

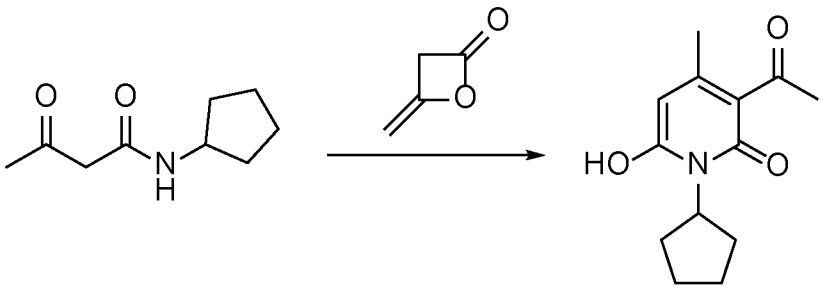
N-cyclopentyl-3-oxo-butanamide (33.8 g, 0.2 moles) was charged into a 1 liter 4 neck RB flask. Tributylamine (3.7 g, 0.02 moles) was added to the RB flask at 25-30°C. The flask was charged with xylene (101 mL). The reaction mixture was headed at 110°C (Bath temperature 130-140°C) for 20-30 min. A solution of 2,2,6-trimethyl-1,3-dioxin-4-one (71 g, 0.5 moles) in xylene (85 mL) was prepared and added to the RB flask. The reaction mixture was heated at 100-110°C for 300 min. The reaction mixture was stirred at 100-110°C for 180 min. The reaction was cooled to 25-30°C. A solution of potassium carbonate (30.4 g) was prepared in DM water (300 mL). The potassium carbonate solution (240 mL) was added to the flask at 25-30°C. The reaction mixture was filtered to remove interfacial material and then allowed to settle for 10 min. The layers were separated. The filtered precipitate was washed with the potassium carbonate solution (60 mL) and the wash layer was added to the organic layer at 25-30°C and stirred for 30 min. The layers were allowed to settle and separated. The aqueous layers were combined and washed with additional xylene (110 mL), then stirred at 25-30°C for 15 min. The layers were allowed to settle for 10 min and separated. The washed aqueous layer was charged into a 1-liter RB flask at 25-30°C. The pH of the aqueous layer was adjusted to pH 1.4-1.6 with concentrated HCl (39 mL). The reaction mass was stirred for 120 min. The reaction was filtered and the solid was washed with MeOH (100 mL). The wet solid was collected at 25-30°C and had a weight of 41.2g. The solid was dried under vacuum in a vacuum oven at 25-30°C for 720-840 min. The dry weight of the crude compound of Formula (VI) was 35 g, with a purity of 62.5 % (by HPLC).

The crude compound of Formula (VI) was obtained as an approximately 4:1 molar ratio of the desired hydroxypyridone to the dehydroacetic acid. The material was

recrystallized from 3 volumes acetonitrile (or 10 volumes methanol) to afford pure compound of Formula (VI) in 50-55% overall molar yield.

Example 2

Alternative preparation of 3-Acetyl-1-cyclopentyl-6-hydroxy-4-methylpuridin-2(1H)-one (Formula VI)



(XI) (VI)

Step 1: Diketene preparation

Acetyl chloride (25 mL,1 eq.) was added dropwise to a stirred solution of triethylamine (55 mL, 1.12 eq.) in diethyl ether (500 mL). The resultant slurry was stirred at room temperature for 16 hrs. The reaction flask was heated at 60 °C and diethyl ether was removed by distillation. The reaction vessel was then cooled, filled with nitrogen, and the collection flask exchanged. The distillation apparatus pressure was reduced to 250-300 torr and the distillation assembly was then lowered into a preheated oil bath (120 °C). A distillation fraction was collected at 53 °C to afford diketene (5.8 g, 43%) as a clear, colorless oil.

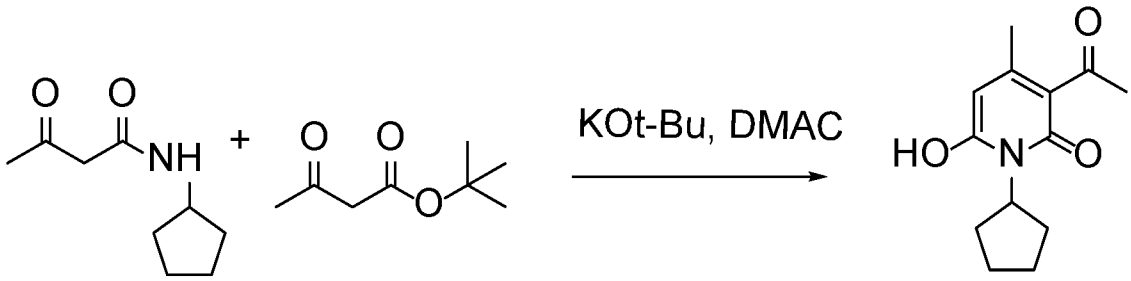
Step 2: Hydroxypyridone preparation

Diketene (0.55 g, 1.1 eq.) was taken in toluene (8 mL,16v) and cooled to 0-5°C. N-Cyclopentyl-3-oxobutanamide (CPA) (0.5 g, 1 eq.), prepared as described in Example 1, was added and the reaction was stirred for about 3.5 hrs. at 0-5°C, and then stirred for 1 hr. at room temperature. N,N-dimethyl aniline (90 mg, 0.12 eq.) was added and washed in with toluene (2 mL, 4v). The reaction mixture was heated to 60°C and diketene (0.8 g, 1.6 eq.) was added in toluene (5 mL, 10v) for 15 min at 60°C. The reaction mixture was heated to reflux at 110°C and the reflux was maintained for 6 hours. After completion of the reaction, the mixture was cooled and 10% aq. potassium carbonate solution (10 mL) added and stirred for 20 min at room temperature. The organic phase was separated and extracted with aq.10% potassium carbonate solution (5 mL). The combined aqueous phase was washed with toluene (5 mL). The aqueous phase was acidified to 1.5 pH using conc. HCl and stirred for 1 hour at room temperature. The mixture was filtered and

washed with water (5 mL). The material was dried under vacuum for 4 hours to obtain pure compound of Formula (VI) (0.35 g, yield:25.2% with respect to CPA) as a pale brown solid.

Example 3

Alternative preparation of 3-Acetyl-1-cyclopentyl-6-hydroxy-4-methylpuridin-2(1H)-one (Formula VI)



(XI) (VI)

An Easymax 402 reactor was charged with N-cyclopentyl-3-oxo-butanamide (XI, 20 g, 118.19 mmol, 100 mass%). Tert-butyl acetoacetate (28.046 g, 177.28 mmol, 100 mass%) was charged into the reaction mass, followed by potassium tert-butoxide (19.893 g, 177.28 mmol, 100 mass%). Dimethylformamide (100 mL, 1293 mmol, 100 mass%) was added to the reactor and the mixture was stirred and heated to a temperature (Tj) of 105°C with stirring at 300 RPM. The reactor was maintained at 105°C with stirring. After 28 hours, an HPLC aliquot indicated incomplete reaction. The mixture was heated and stirred for an additional 20 hours. After 48 hours, an aliquot was tested by HPLC and the reaction was stopped.

The reaction mixture was unloaded and stored at 25 °C to 30°C. The mixture was quenched by addition of 300 mL 1N HCl solution. 300 mL toluene was added, and the mixture was stirred for 15 minutes. The layers were allowed to settle and separate, and the mixture was extracted with 100 mL toluene. The layers were separated, and the combined organic layer was washed with 300 mL DM water. The layers were separated again, and the combined toluene layer was stored at 25 to 30°C.

The toluene layer was transferred to a 1L round bottom (RB) flask. A solution of potassium carbonate (17.968 g, 130.01 mmol, 100 mass%) in 180mL DM water was prepared. The 10% potassium carbonate solution was added to the toluene layer and stirred for 30 minutes. The reaction mass was filtered, and the layers were allowed to settle and were separated. The toluene layer was stirred for 30 minutes with an additional 60mL portion of 10% potassium carbonate solution. The layers were allowed to settle and

were separated. The toluene layer was collected and stored for quantification: Weight = 398.7g and volume = 460mL.

The combined aqueous layers were washed with 90 mL toluene, and the toluene wash layer was separated and stored for quantification: Weight = 100.1g and volume = 108mL.

The combined aqueous layers were charged into a 1L RB flask. 200mL toluene was added and the pH of the aqueous layer was adjusted to pH 2 with 40 mL concentrated HCl. The mixture was stirred for 10 minutes. The layers were allowed to settle and were separated. The aqueous layer was extracted again with 80 mL toluene while maintaining the pH. The layers were separated, and the toluene wash layer was stored for quantification: Weight = 411.4g and volume = 398mL.

The organic layers were combined, and the toluene was distilled in a rotary evaporator to provide the crude product. Crude weight =19.7g.

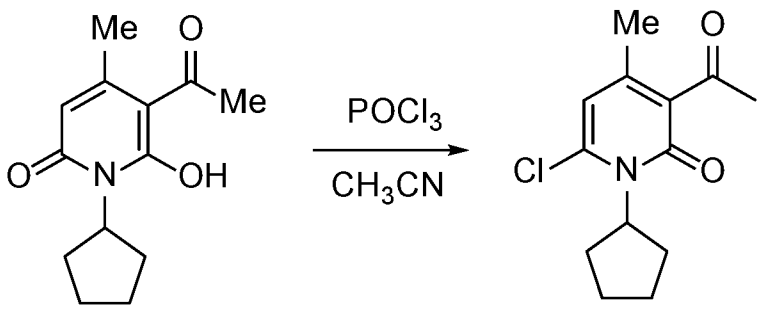
The crude mass was charged into a 500 mL4N RB and methanol (110 mL, 2718.9 mmol, 100 mass%) was added. The crude mass was heated to reflux and stirred to provide a clear solution. The heating was switched off and the mass cooled gradually to 30°C. The mass was cooled further to 0°C and stirred for 1 hour at 0 to 5°C.

The solid was filtered and washed with 20mL methanol. The toluene layer was stored for quantification: Weight = 94.5g and volume = 115mL.

The semi-dried solid was unloaded and dried in a vacuum oven overnight at 25 to 30°C. Wet weight = 7.5g. After drying, the dried solid was unloaded and packed in a poly bag. Dry weight = 7.2g. The compound of Formula (VI) was obtained in 25.9% yield after crystallization. The material was consistent with an authentic sample of Formula (VI).

Example 4

Preparation of 3-acetyl-6-chloro-1-cyclopentyl-4-methylpyridin-2(1H)-one (Formula VII)



(VI) (VII)

Procedure & Conditions:

$POCl_3$ (19.8 mL, 5 equiv.) was added to the solution of the compound of Formula (VI) (10 g, 1 eq..) in ACN (40 mL) and the reaction was heated at 80°C for 1 hour. The mixture was poured into ice/water, then sat. $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The product purified by column chromatography (EtOAc:petroleum ether = 1:8). The compound of Formula (VII) was isolated as a light yellow oil 8.4 g (80%). The crude product was used without further purification.

The reaction was alternatively conducted under neat conditions (using 20 eq. of $POCl_3$).

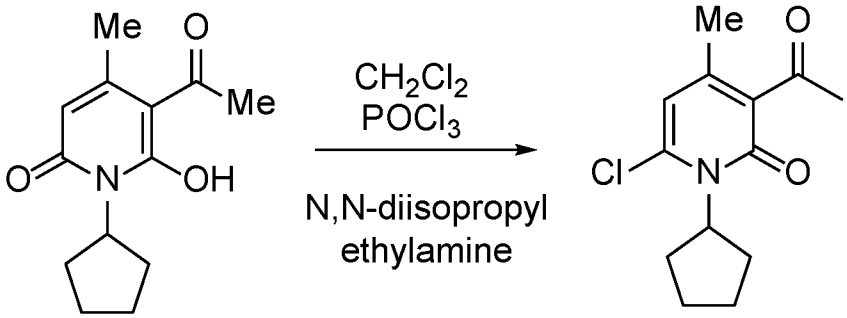
Results & Characterization:

^1H NMR (400 MHz, Chloroform-*d*) δ: 6.15 (s, 1H), 5.39 – 5.26 (m, 1H), 2.49 (s, 3H), 2.35 – 2.23 (m, 2H), 2.13 (s, 3H), 2.06 – 1.95 (m, 2H), 1.91 – 1.82 (m, 2H), 1.66 – 1.55 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.3, 161.4, 149.1, 138.8, 129.0, 111.0, 60.2, 31.3, 28.6, 25.9, 19.7.

Example 5

Alternative preparation of 3-acetyl-6-chloro-1-cyclopentyl-4-methylpyridin-2(1H)-one (Formula VII)



(VI) (VII)

Procedure & Conditions:

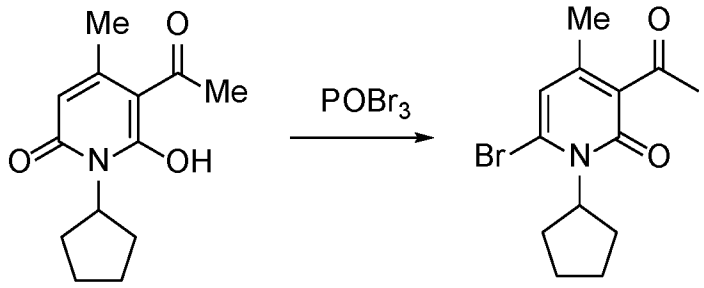
$POCl_3$ (65.2g, 1.0 equiv.) and N,N-diisopropylethylamine (54.9g, 1.0 equiv.) were added to the solution of the compound of Formula (VI) (100 g, 1.0 equiv.) in dichloromethane (500 mL) at 25-30 °C and the reaction was heated to reflux for 24 hour. After reaction completion, cooled to 25°C and water (1000mL) and dichloromethane (500mL) were added into the reaction mixture. The pH of the reaction mixture adjusted to 7.0 using solid sodium bicarbonate (105g) and stirred for 30min at 25-30°C. Layers were separated and aqueous layer was back extracted with dichloromethane (500mL). Combined the organic layer and evaporated the solvent under vacuum at 40°C to obtain

the compound of Formula (VII) as dark pink residue (114.1g, 91.5% yield from VI after assay correction). The crude product was used without further purification.

Example 6

Preparation of 3-acetyl-6-bromo-1-cyclopentyl-4-methylpyridin-2(1H)-one

(Formula VIII)



(VI) (VIII)

Procedure & Conditions:

$POBr_3$ (4.9 g, 2 equiv.) was added to the solution of the compound of Formula (VI) (2 g, 1equiv.) in ACN (20mL) and the reaction was heated at 80°C for 30 min. The mixture was poured into ice/water and extracted with EtOAc. The product purified by column chromatography (EtOAc: petroleum ether = 1:6). The compound of Formula (VIII) was isolated as a light brownish oil 1.7 g (67%). The crude product was used without further purification.

Results & Characterization:

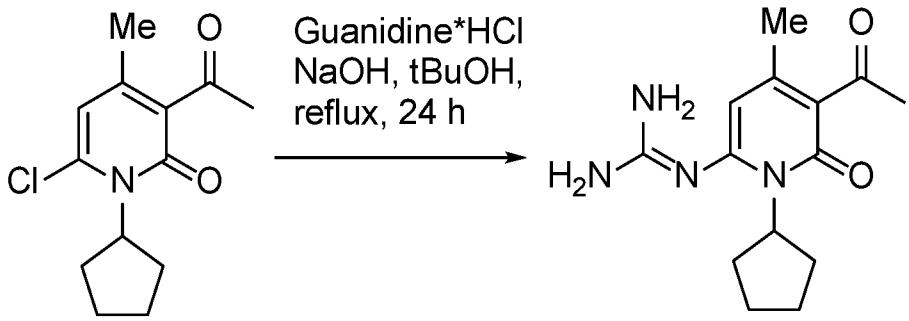
^{1}H NMR (400 MHz, Chloroform-*d*) δ: 6.35 (s, 1H), 5.18 (tt, *J* = 9.3, 7.9 Hz, 1H), 2.48 (s, 3H), 2.36 – 2.24 (m, 2H), 2.11 (s, 3H), 2.07 – 1.94 (m, 2H), 1.88 – 1.73 (m, 2H), 1.64 – 1.52 (m, 2H).

^{13}C NMR (101 MHz, CDCl3) δ 202.36, 160.90, 149.13, 129.66, 129.24, 115.19, 64.84, 31.28, 28.47, 25.97, 19.45.

Example 7

Preparation of 2-(5-acetyl-1-cyclopentyl-4-methyl-6-oxo-1,6-dihydropyridin-2-yl)guanidine

(Formula IV)



(VII) (IV)

Procedure & Conditions:

A suspension of guanidine hydrochloride (11.3 g, 3.5 eq.) and NaOH (4.7 g, 3.5 eq.) in *t*-BuOH (160 mL) was stirred at rt. After 1 hour, a solution of compound of Formula (VII) (8.5 g, 1 eq.) in t-BuOH (20 mL) was added and the mixture was refluxed overnight. After cooling to rt; H_2O (100 mL) was added. The product was filtered, washed with H_2O and dried under vacuum. The compound of Formula (IV) was isolated as a yellow solid: 6.2g (67%).

The reaction was alternatively conducted using KO*t*Bu (3 eq.) as base in *t*-BuOH with guanidine hydrochloride (3 eq.). The compound of Formula (IV) was isolated: 100 mg (93%).

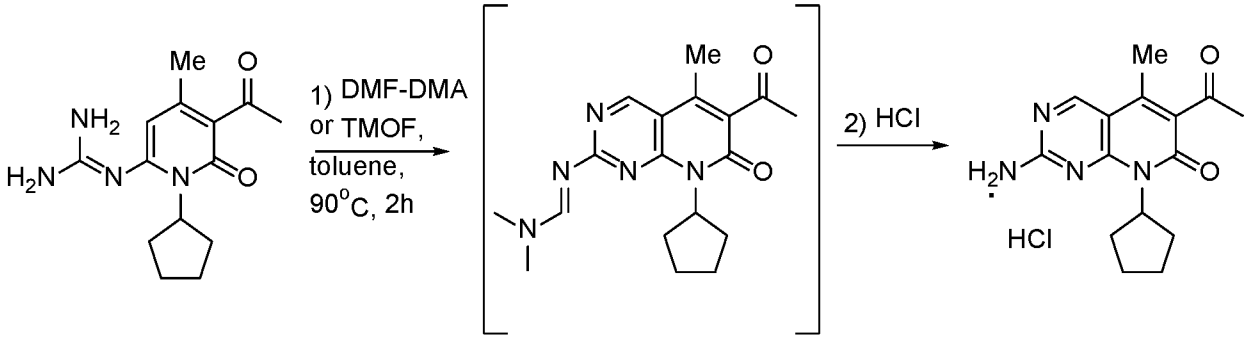
Results & Characterization:

^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.29 (bs, 4H), 5.56 (p, J = 8.8 Hz, 1H), 5.45 (s, 1H), 2.36 (s, 3H), 2.23 – 2.14 (m, 2H), 2.10 (s, 3H), 1.95 – 1.83 (m, 2H), 1.66 – 1.56 (m, 2H), 1.54 – 1.43 (m, 2H).

^{13}C NMR (101 MHz, DMSO) δ: 200.18, 163.31, 157.36, 157.16, 152.02, 115.14, 99.96, 53.35, 32.49, 28.54, 26.23, 22.15.

Example 8

Preparation of 6-acetyl-2-amino-8-cyclopentyl-5-methylpyrido[2,3-d]pyrimidin-7(8H)-one (Formula II) hydrochloride salt



(IV) (X) (II)

Procedure & Conditions:

Dimethylformamide dimethylacetal (DMF-DMA) (5.5 mL, 1.9 eq.) was added to a suspension of compound of Formula (IV) (6.07 g, 1 equiv) in toluene (150 mL). The reaction mixture was heated at 90°C for 2 hours (full conversion to the compound of Formula (II) and the compound of Formula (X) (where Y is $N(CH_3)_2$) was observed by UPLC/MS). After cooling to rt, conc. HCl (8 mL, ~4-5 eq.) was added dropwise and reaction mixture was heated at 50°C for 2-4 hours (until all intermediate enamine of Formula (X) was hydrolyzed). The reaction mixture was cooled to rt, the product was filtered, and washed with EtOAc (or cold MeOH). The product was dried under vacuum. The compound of Formula (II) was isolated as a light yellow solid: 5.96 g (95%).

Results & Characterization:

^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.80 (s, 1H), 7.54 (s, 2H), 5.85 (p, J = 8.8 Hz, 1H), 2.40 (s, 3H), 2.25 (s, 3H), 2.25 – 2.10 (m, 2H), 2.08 – 1.90 (m, 2H), 1.84 – 1.67 (m, 2H), 1.65 – 1.49 (m, 2H).

^{13}C NMR (101 MHz, DMSO) δ: 202.49, 161.25, 157.10, 156.72, 153.35, 142.53, 129.96, 106.07, 53.09, 31.75, 28.29, 25.96, 14.19.

Elemental analysis for crystallized product (from MeOH):

N = 18.2732; C = 58.8557; H = 6.0344

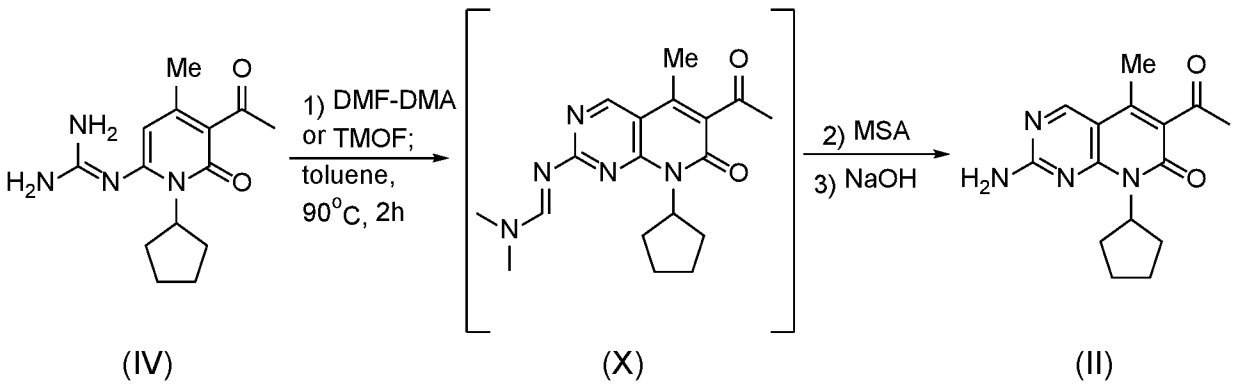
N = 18.40; C = 59.16; H = 6.12 (calc. Formula (II) *0.5HCl)

N = 19.57; C = 62.92; H = 6.34 (calc. Formula (II))

N = 17.36; C = 55.81; H = 5.93 (calc. Formula (II) *HCl)

Example 9

Preparation of 6-acetyl-2-amino-8-cyclopentyl-5-methylpyrido[2,3-d]pyrimidin-7(8H)-one (Formula II)



(IV) (X) (II)

Procedure & Conditions:

Dimethylformamide dimethylacetal (DMF-DMA) (36.3g, 1.9 equiv.) was added to a suspension of compound of Formula (IV) (44.3g, 1.0 equiv.) in toluene (842mL). The reaction mixture was heated at 90°C for 2 hours (full conversion to the compound of Formula (II) and formylated compound of Formula (X) was observed by UPLC/MS). After cooling to 60-65°C and water (443mL), methane sulfonic acid (46.2g, 3.0 equiv.) were slowly added for 20 min and stirred for 4 hours. After completion of reaction, cooled to 25-30°C and layers were separated. Added water (222 mL) and methane sulfonic acid (15.6g, 1.0 equiv.) into organic layer and stirred for 30min at 25-30°C. Layers were separated and combined the aqueous layers and organic layer was repeated the extraction for another two times as above with same amount of water (222mL) and methane sulfonic acid (15.6g, 1.0 equiv.). Combined all aqueous layers and adjusted the pH 7.05 using aqueous 50%sodium hydroxide solution (76mL) over 30 min at 25-30°C and stirred for 1 hour. Filtered the solid and washed with water (50mL * 3times). Dried the product under vacuum at 25-30°C for 16 hours to obtain the crude compound of Formula (II) as yellow solid (41.2g, 87.6% yield after assay correction).

The purification of crude compound (II): N-propanol (410mL) was added to crude compound (II) (41.0 g) at 25-30°C and heated to 90°C. The solution held at 90°C for 30 min to obtain at clear solution and cooled to 0-5°C over 4 hour and stirred for 1 hour. Filtered the solid and washed with chilled n-propanol (82mL) followed by chilled MTBE (82mL). Dried the material under vacuum at 25-30°C to obtain the pure compound of Formula (II) as yellow solid (37.0g, 79.3% yield after assay correction). Purity 98.61% (area%; HPLC).

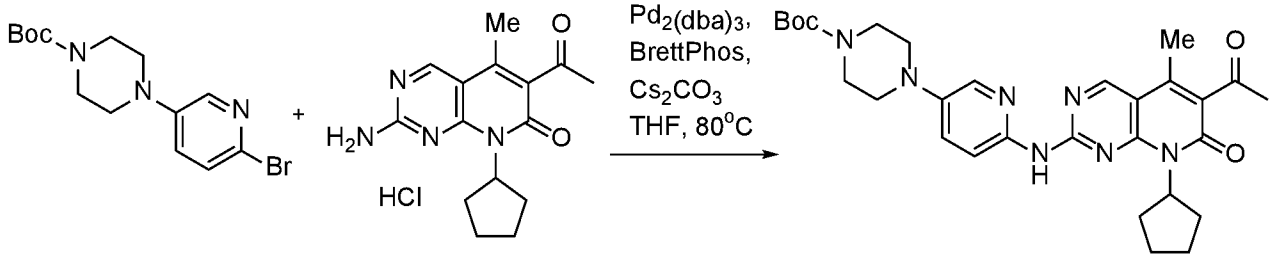
^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.76 (s, 1H), 7.34 (s, 2H), 5.87 (p, J = 8.0 Hz, 1H), 2.39 (s, 3H), 2.25 (s, 3H), 2.23 – 2.14 (m, 2H), 2.04 – 1.94 (m, 2H), 1.78 – 1.70 (m, 2H), 1.61 – 1.51 (m, 2H).

^{13}C NMR (101 MHz, DMSO) δ: 202.68, 162.68, 160.84, 158.72, 155.11, 142.49, 127.82, 104.84, 51.92, 31.37, 27.79, 25.56, 13.55.

LCMS: $C_{15}H_{19}N_4O_2^+$ Exact Mass $[M+H]^+$: 287.1503; found 287.1498

Example 10

Preparation of tert-butyl 4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazine-1-carboxylate (Formula I)



(III-a) (II) (I)

The compound of Formula (III-a) (250 mg, 1 eq) and the compound of Formula (II) (259 mg, ~1 eq.) were suspended in THF (6 mL) in a vial. $Pd_2(dba)_3$ (35 mg, 5 mol %), BrettPhos (40 mg, 10 mol %) and Cs_2CO_3 (715 mg, 3 eq) were added under argon. The mixture was heated under argon at 80°C overnight. The reaction was monitored by UPLC. After 17 hours, the compound of Formula (III-a) was not detected and the reaction mixture contained the compounds of Formulae (IV) (6%) and (I) (~70%). The reaction was worked up by filtering through a pad of CELITE, washing with DCM, evaporating the solvent and purifying by column chromatography (EtOAc:DCM:MeOH=1:1:2%). The compound of Formula (I) was isolated as an orange solid: 255 mg (65%). By UPLC and NMR, the product Formula (I) as the major product (ca. 90%), containing residual starting material of Formula (II) (ca. 10%).

As shown in Table 1, in a second run (Reaction 2), using the same catalyst and ligand, the compound of Formula (I) was isolated in ~77% yield after 16 hours. In a third run (Reaction 3), using the same catalyst and the Xanphos ligand, the compound of Formula (I) was isolated in ~55% yield with significant residual starting materials after 16 hours.

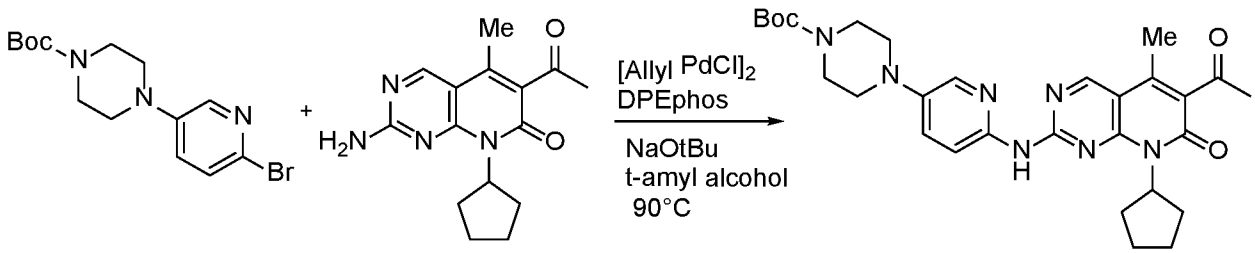
Table 1

Reaction	III-a:II (eq)	Catalyst (eq)	Ligand (eq)	Base (eq)	Solvent (1mL), temp.	Observations UPLC or NMR
2	1 : 1	$Pd_2(dba)_3$ (5 mol%)	BrettPhos (10 mol%)	Cs_2CO_3 (3)	THF, 80°C	UPLC (16 h): II (not detected) III-a (1%) I (77%) and imps

						NMR crude ($CDCl_3$): II : I ⩽ 0.1 : 1
3	1 : 1	$Pd_2(dba)_3$ (5 mol%)	Xanphos (10 mol%)	Cs_2CO_3 (3)	THF, 80°C	UPLC (16h): II (31%) III-a (10%), I+m/z 525 (55%) and imps

Example 11

Alternative preparation of tert-butyl 4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazine-1-carboxylate (Formula I)



(III-a) (II) (I)

The compound of Formula (III-a) (59.7g, 1.0 equiv.) and the compound of Formula (II) (50g, 1.0 equiv.) were suspended in t-amyl alcohol (1000mL) under nitrogen atmosphere. Bis[2-(diphenylphosphino)-phenyl]ether (DPEphos) (3.29g, 0.035equiv.) and allylpalladium (II) chloride dimer (0.815g, 0.0125equiv.) and sodium-t-butoxide (25.2g, 1.5equiv.) were added under nitrogen atmosphere and the reaction mixture was purged with nitrogen for 15-20 min at 25-30°C. Replaced the nitrogen purging with nitrogen atmosphere and heated the reaction mixture to 90°C and stirred for 3-4 hours under nitrogen atmosphere. After completion of reaction, cooled the reaction mixture to 80-82°C. Acetic acid (10.5g, 1.0eq) in water (100mL, 2v) was added over 10 min at 80-82°C and stirred for 2.0 hours. The reaction mixture was cooled to 10°C over 45 min to 60 min and stirred for 15min. Filtered the solid and washed with t-amyl alcohol (250mL) and methyl tertiary butyl ether (500mL). The material dried under vacuum in Buckner funnel about 3-5Hr to obtain a product Formula (I) as yellow wet solid (91.3g, 80% yield after assay correction). Purity 97.78% (area%; HPLC).

^1H NMR (400 MHz, $CDCl_3$) δ: 9.17-9.14 (brs, 1H), 8.87 (s, 1H), 8.17 (d, J = 9.2 Hz, 1H), 8.06 (d, J = 4.0 Hz, 1H), 7.32 (dd, J = 8.0 Hz, J = 4.0 Hz, 1H), 5.86 (p, J = 8.0 Hz,

1H), 3.61 (dd, J = 4.0 Hz, 4H), 3.14 (d, J = 4.0 Hz, 4H), 2.55 (s, 3H), 2.39 (s, 3H), 2.37 – 2.20 (m, 2H), 2.09 – 2.04 (m, 2H), 1.90 – 1.87 (m, 2H), 1.61 – 1.31 (m, 2H), 1.49 (s, 9H). LCMS: $C_{29}H_{38}N_7O_4^+$ Exact Mass $[M+H]^+$: 548.2985; found 548.2958

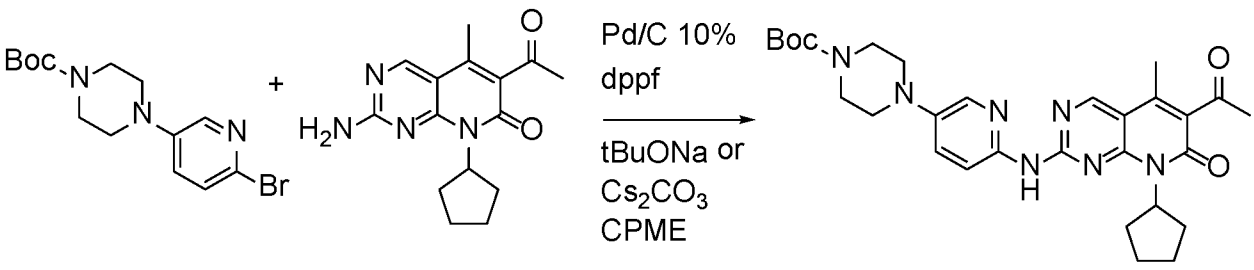
As shown in Table 2, using the same catalyst under reaction conditions as above, screened the solvents, ligands and bases in a 1.0 mmol scale to obtain the compound of Formula (I). The best conditions were used above for the 50 g scale.

Table 2.

Ligand	Solvent	HPLC Yield of Cpd (I) with Cs_2CO_3	HPLC Yield of Cpd (I) with NaO^tBu
Xanthphos	Dioxane	51	81
Xanthphos	m-xylene	21	87. 4 (80)
Xanthphos	tertiary amylalcohol	--	71 (81)
Xanthphos	Toluene	--	65.2
t-Bu XPhos	tertiary amylalcohol	55	89 (96.1 & 90.1)
t-Bu XPhos	m-xylene	12.4	46.1
t-Bu XPhos	Dioxane	5	8
t-Bu XPhos	toluene	--	72.1
JohnPhos	tertiary amylalcohol	26	80
JohnPhos	m-xylene	2.4	56.2
JohnPhos	Dioxane	40	65
DPEphos	tertiary amylalcohol	12	94.7 (94.5 & 92.7)
DPEphos	m-xylene	13.4	82.5
DPEphos	Dioxane	20	60
DPEphos	toluene	--	69.5

Example 12

Alternative preparation of tert-butyl 4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazine-1-carboxylate (Formula I)



(III-a) (II) (I)

tBuONa base:

In a microwave (MW) vial, the compound of Formula (III-a) (239.0 mg, 1 eq), the compound of Formula (II) (200.0 mg, 1 eq), tBuONa (100.7 mg, 1.5 eq), Pd/C 10% (14.9 mg, 0.02 eq) and 1,1'-bis(diphenylphosphino)ferrocene (dppf) (11.6 mg, 0.03 eq) were suspended in 3 mL CPME. The mixture was degassed (Schlenk line 5x). The reaction mixture was heated overnight (~16h) at 120°C under argon. The reaction mixture was cooled to rt and poured into DCM/H_2O. The mixture was extracted with DCM, dried, filtered and evaporated to provide the compound of Formula (I). NMR with internal standard (1,3,5-trimethoxybenzene, TMB) 35% Yield.

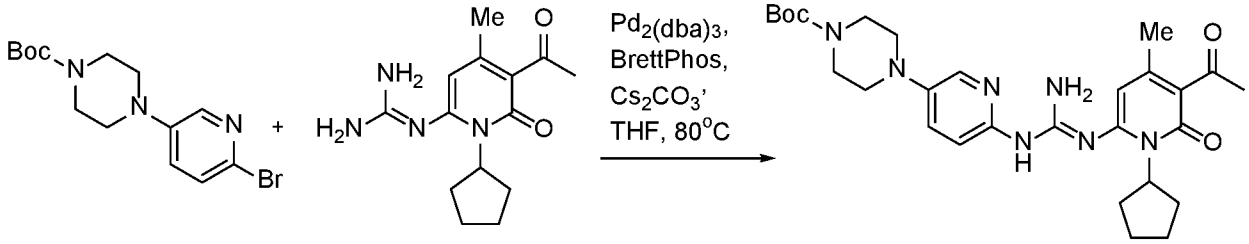
Cs_2CO_3 base:

In a MW vial, the compound of Formula (III-a) (239.0 mg, 1 eq), the compound of Formula (II)(200.0 mg, 1 eq), Cs_2CO_3 (341.4 mg, 1.5 eq), Pd/C 10% (14.9 mg, 0.02 eq) and dppf (11.6 mg, 0.03 eq) were suspended in 3 mL CPME. The mixture was degassed (Schlenk line 5x). The reaction mixture was heated overnight (~16h) at 120°C under argon. The reaction mixture was cooled to rt and poured into DCM/H_2O. The mixture was extracted with DCM, dried, filtered and evaporated to provide the compound of Formula (I). NMR with internal standard (TMB) 87% Yield. The crude product was purified by column chromatography (eluent Pet:EtOAc 1:1 – 0:1). The compound of Formula (I) was isolated: 360 mg (94%); Purity 92% (LCMS).

Example 13

Preparation of tert-butyl (E)-4-(6-(2-(5-acetyl-1-cyclopentyl-4-methyl-6-oxo-1,6-dihydropyridin-2-yl)guanidino)pyridin-3-yl)piperazine-1-carboxylate

(Formula V)



(III-a) (IV) (V)

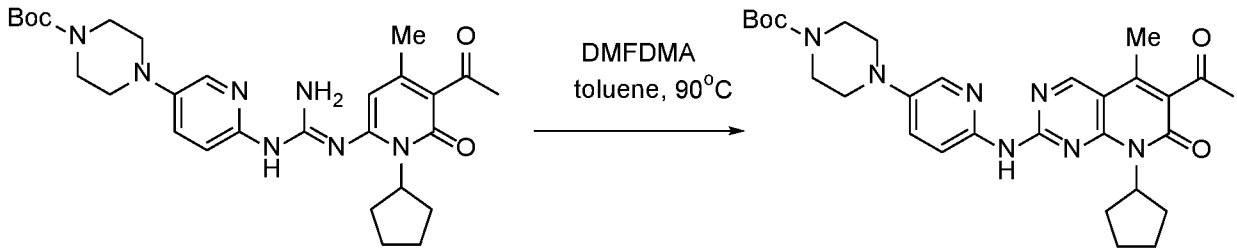
The compound of Formula (IV) (200 mg) was combined with the compound of Formula (III-a) (1 eq) in THF (6 mL) under Argon. $Pd_2(dba)_3$ (5 mol%), BrettPhos (10 mol%), and Cs_2CO_3 (2equiv) were added and the reaction mixture was heated under argon at 80°C. After 16 hours, the ratio of starting material ofl formula (IV) to product of Formula (V) was ~0.1 : 1 by NMR and UPLC. The compound of Formula (V) was isolated by filtration through a pad of CELLITE, washing with DCM, evaporation and purification by column chromatography (EtOAc: DCM: MeOH = 1: 1: 2%): 0.22g (57%).

Other ligands, including XantPhos, Amphos,DavePhos, RuPhos, S-Phos, DPE-Phos, and MePhos were used. The compound of Formula (V) was obtained in lower yields using these ligands, with the diarylated product observed as a major impurity.

Example 14

Alternate preparation of tert-butyl 4-(6-((6-acetyl-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)pyridin-3-yl)piperazine-1-carboxylate

(Formula I)



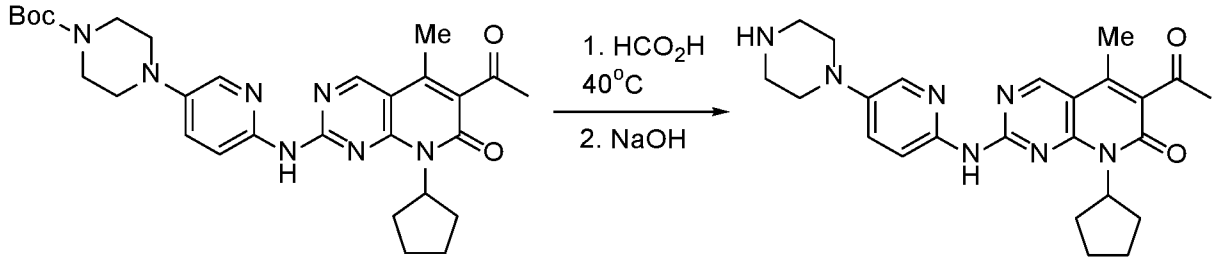
(V) (I)

The compound of Formula (V) (30 mg, 1 eq) was combined with DMF-DMA (10μL, 1eq) in toluene (5 mL) and heated at 90°C. After 30 min, about 20% of starting material remained by UPLC. After 3 hours, the reaction had reached full conversion to material with m/z 548. The mixture was evaporated. The product was filtered through silica

(EtOAc:DCM (1:1)+5% MeOH). The compound of Formula (I) was isolated as the product as a yellow solid. ^{1}H, ^{13}C, HSQC, and HMBC NMR were consistent with authentic samples of Formula (I).

Example 15

Preparation of 6-acetyl-8-cyclopentyl-5-methyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (Palbociclib)



(I) Palbociclib

Formic acid (8mL) was added to the neat compound of Formula (**I**) (2.0 g, 1.0 equiv.) under nitrogen atmosphere. The resulted mixture was heated to 40-42°C over 5 to 10 min. and then stirred for 1.5 to 2.0 h. After completion of reaction, the reaction mixture was diluted with water (15 mL). The resulted aqueous solution was extracted with CH2Cl2, EtOAc, ^{i}PrOAc or Anisole (25 ml *2 times) at 50-65°C to remove the impurities. The aqueous layer was adjusted to ca. pH 12.5 using 33% (w/w) aq. sodium hydroxide (30 mL) over 30 min at 40°C. The resulted slurry was cooled to 15°C over 50 min to 80 min and stirred for 30 min at 15°C. Filtered the solid and washed with water (20mL). Dried the material under vacuum at 25°C for 16Hr to obtain the Palbociclib as yellow solid (1.7g, 94% yield after assay correction). Purity 98.13% (area%; HPLC).

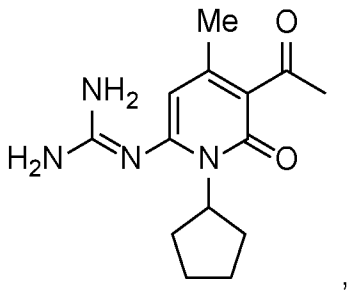
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (s, 1H),), 8.33-8.32 (brs, 1H), 8.12 (dd, J = 9.6 Hz; J = 4.0 Hz 1H), 8.00 (d, J = 4.0 Hz, 1H), 7.28 (dd, J = 8.0 Hz, J = 4.0 Hz, 1H), 5.81 (p, J = 8.0 Hz, 1H), 3.86-3.77 (brs, 0.54H) 3.45 (t, J = 4.0 Hz, 1H); 3.26-3.22 (brs, 0.3H); 3.17-3.12 (m, 4H), 3.08-2.5 (m, 3H), 2.48 (s, 3H), 2.34 (s, 3H), 2.29 – 1.20 (m, 2H), 2.06 – 1.95 (m, 2H), 1.88 – 1.74 (m, 2H), 1.74 – 1.55 (m, 2H).

LCMS: $C_{24}H_{30}N_7O_2^+$ Exact mass $[M+H]^+$= 448.2461; found 448.2446

CLAIMS

What is claimed is:

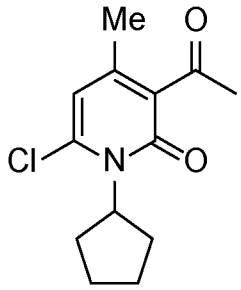
1. A process for the preparation of the compound of Formula (IV):



(IV)

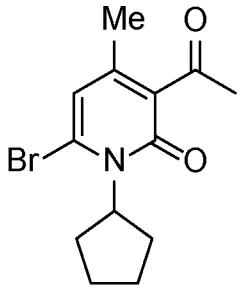
comprising:

(a) reacting a compound of Formula (VII) or (VIII):



(VII)

or



(VIII)

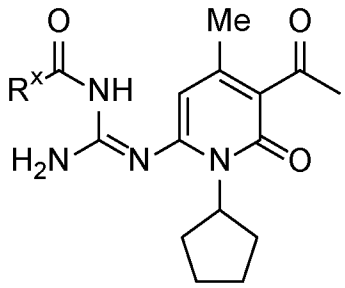
with a guanylation reagent and a base in a suitable solvent;

to provide the compound of Formula (IV).

2. The process of claim 1, wherein the guanylation reagent is a guanidine salt or an N-acyl guanidine.

3. The process of claim 2, wherein the guanylation reagent is a guanidine salt selected from the group consisting of guanidine hydrochloride, guanidine carbonate salt and guanidine hydrogen carbonate.

4. The process of claim 2, wherein the guanylation reagent is an N-acyl guanidine of formula $R^xC(O)N=C(NH_2)_2$, where R^x is H, C_1-C_4 alkyl, optionally substituted phenyl or optionally substituted benzyl, and step (a) provides an intermediate of Formula (IV^x):



(IV^x)

where R^x is H, C_1-C_4 alkyl, optionally substituted phenyl or optionally substituted benzyl; and the process further comprises:

(b) hydrolyzing the compound of Formula (IV^x) with base;

to provide the compound of Formula (IV).

5. The process of claim 6, wherein the guanylation reagent is N-formyl guanidine.

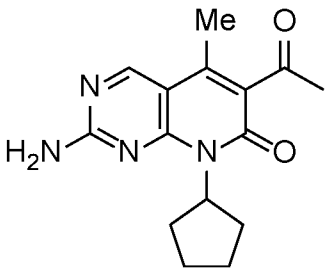
6. The process of any one of claims 1 to 7, wherein the base is an alkali metal hydroxide, alkoxide or carbonate base, or an alkaline earth hydroxide, alkoxide or carbonate base.

7. The process of claim 6, wherein the base is sodium hydroxide, sodium tert-butoxide, sodium tert-pentoxide, potassium hydroxide, potassium tert-butoxide, potassium tert-pentoxide, potassium carbonate or cesium carbonate.

8. The process of any one of claims 1 to 7, wherein the solvent comprises a tertiary alcohol.

9. The process of claim 8, wherein the solvent is tert-butanol or tert-amyl alcohol.

10. A process for the preparation of the compound of Formula (II):

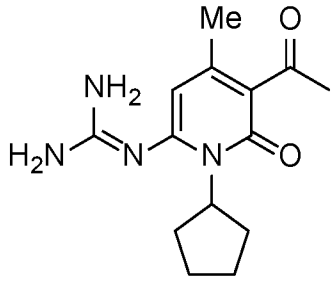


(II)

or a salt thereof,

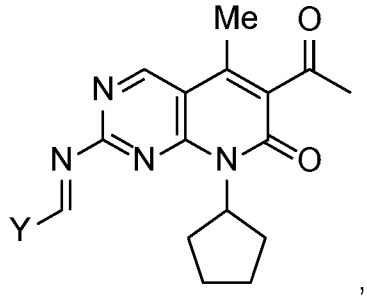
comprising:

(a) reacting a compound of Formula (IV) prepared by the process of any one of claims 1 to 9:



(IV)

with a formylation reagent in a suitable solvent under dehydrative conditions to provide a compound of Formula (X):



(X)

wherein the formylation reagent is a di(C_1-C_4 alkyl)formamide di(C_1-C_4 alkyl) acetal or a tri(C_1-C_4 alkyl) orthoformate, and Y is N(C_1-C_4 alkyl)$_2$ or O(C_1-C_4 alkyl);

(b) optionally isolating the compound of Formula (X); and

(c) hydrolysis of the compound of Formula (X) in the presence of an acid in a suitable solvent to provide the compound of Formula (II), or a salt thereof.

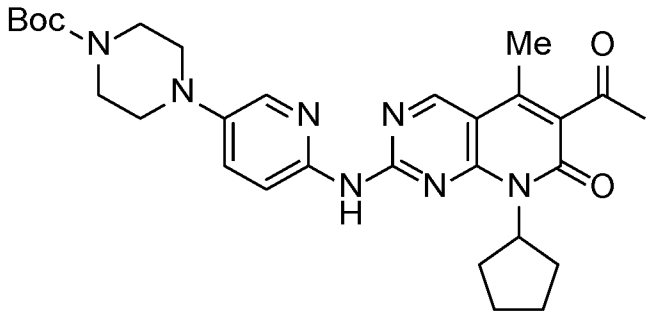
11. The process of claim 10, wherein the formylation reagent in step (a) is a formic acid ortho ester or a formamide acetal selected from N,N-dimethyl formamide dimethyl acetal (DMF-DMA)] and trimethyl orthoformate (TMOF).

12. The process of claim 10 or 11, wherein the solvent in step (a) is an aromatic hydrocarbon and the dehydrative conditions in step (a) comprise heating the solution comprising the compound of Formula (IV) and the formylation reagent at about 90ºC for about 2 hours.

13. The process of any one of claims 10 to 12, wherein the acid in step (c) is an organic or inorganic acid.

14. The process of claim 13, wherein the acid in step (c) is aqueous hydrochloric acid (HCl) and the hydrolysis in step (c) comprises heating a solution comprising the compound of Formula (X) and HCl at about 50ºC for about 2-4 hours.

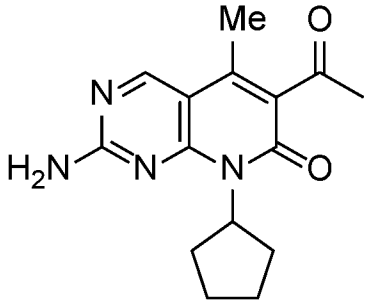
15. A process for the preparation of the compound of Formula (I):



(I) ,

comprising:

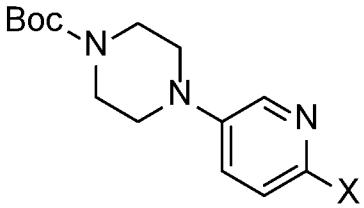
(a) coupling a compound of Formula (II) prepared by the process of any one of claims 10 to 14:



(II)

or a salt thereof,

with a compound of Formula (III):

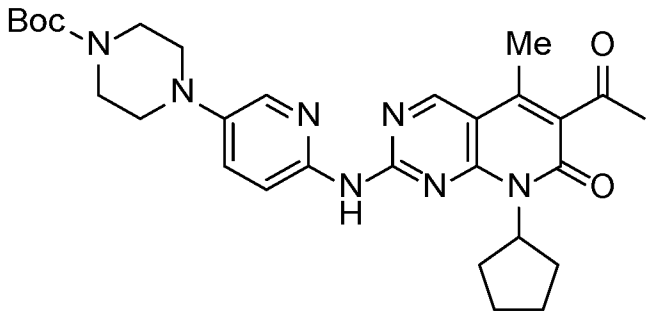


(III)

where X is a leaving group selected from a halo and a sulfonate ester,

in the presence of a transition metal catalyst, a base, and optionally a ligand, in a suitable solvent to provide the compound of Formula (I).

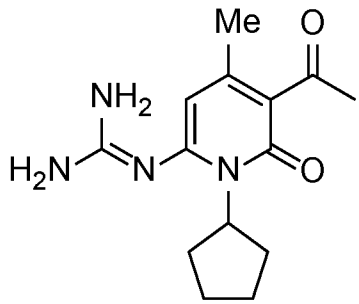
16. A process for the preparation of the compound of Formula (I):



(I)

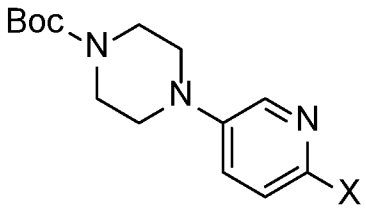
comprising:

(a) coupling a compound of Formula (IV) prepared by the process of any one of claims 1 to 9:



(IV)

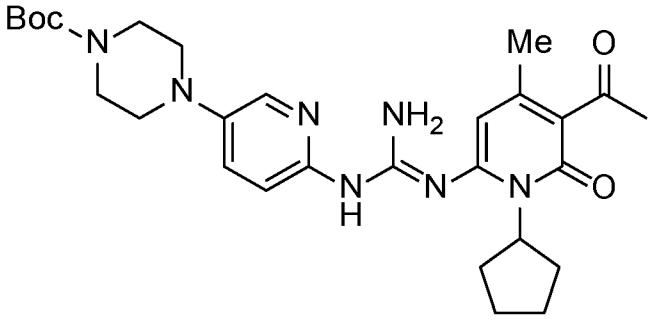
with a compound of Formula (III):



(III)

where X is a leaving group selected from a halo and a sulfonate ester,

in the presence of a transition metal catalyst, a base, and optionally a ligand, in a suitable solvent to provide the compound of Formula (V):



; and

(V)

(b) reacting the compound of Formula (V) with a formylation reagent in a suitable solvent under dehydrative conditions to provide a compound of Formula (I),

wherein the formylation reagent is a di(C_1-C_4 alkyl)formamide di(C_1-C_4 alkyl) acetal or a tri(C_1-C_4 alkyl) orthoformate.

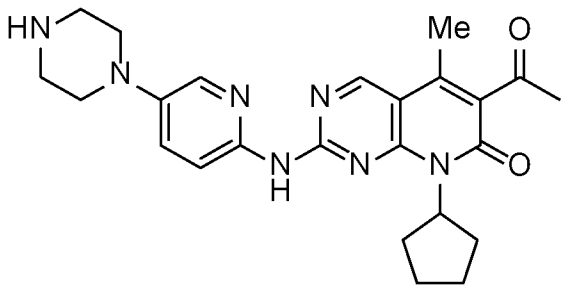
17. The process of claim 15 or 16, wherein X is Br.

18. The process of any one of claims 15 to 17, wherein the transition metal catalyst is a palladium catalyst or a copper catalyst.

19. The process of claim 18, wherein step (a) further comprises a ligand.

20. The process of any one of claims 15 to 19, wherein the base in step (a) is an alkali metal carbonate, alkali metal alkoxide, alkali metal phosphate, alkaline earth carbonate, alkaline earth alkoxide or alkaline earth phosphate base.

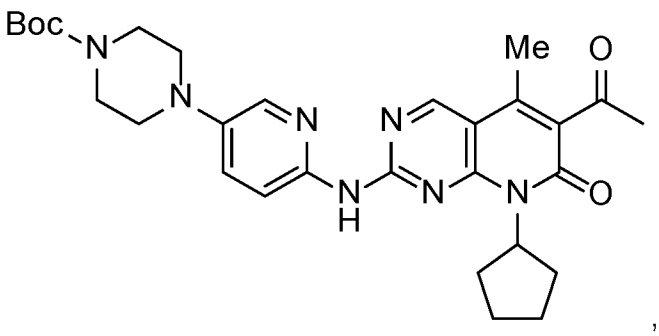
21. A process for the preparation of palbociclib:



,

comprising:

(a) reacting the compound of Formula (I) prepared by the process of any one of claims 15 to 20:



,

(I)

with formic acid; and

(b) diluting the reaction mixture with water, washing the aqueous layer with one or more organic solvents, and then adjusting the pH of the aqueous phase to basic pH with base to provide palbociclib (free base).

22. The process of claim 21, wherein the process further comprises: (c) cooling the mixture in step (b) to provide a slurry and filtering to isolate palbociclib.

23. The process of claim 21 or 22, wherein the mixture of formic acid and the compound of Formula (I) in step (a) is heated to about 40°C under nitrogen atmosphere until completion of reaction.

24. The process of any one of claims 21 to 25, wherein step (b) comprises washing the aqueous phase with one or more organic solvents, and adjusting the pH of the aqueous layer to about pH 12.5 with aqueous base.

25. The process of any one of claims 21 to 24, wherein the process further comprises: (c) isolating palbociclib by gradually cooling the resulting slurry in step (b) to about 15°C and then filtering and washing the solid material with water; and optionally (d) drying the solid material under vacuum at about 25°C to obtain palbociclib.

26. The process of claim 25, further comprising: (e) crystallizing the free base of palbociclib from a suitable solvent to provide crystalline palbociclib free base (Form A), having:

(1) a powder X-ray diffraction pattern comprising peaks at diffraction angles (2θ) of: (a) 8.0 ± 0.2, 10.1 ± 0.2 and 11.5 ± 0.2 2θ; or (b) 8.0 ± 0.2, 10.1 ± 0.2, 10.3 ± 0.2, and 11.5 ± 0.2 2θ;

(2) a ^{13}C solid state NMR spectrum comprising resonance (ppm) values of: (a) 12.5 ppm ± 0.2 ppm; (b) 12.5 ppm and 112.4 ppm ± 0.2 ppm; or (c) 12.5 ppm, 112.4 ppm and 143.2 ppm ± 0.2 ppm;

(3) a primary particle size distribution characterized by a D90 value of from about 30 μm to about 65 μm; or

(4) a D[4,3] value of from about 15 μm to about 30 μm;

or any combination of two or more of (1)(a), (1)(b), (2)(a), (2)(b), (2)(c), (3), or (4).

27. The process of claim 26, wherein the crystallization solvent in step (e) is a mixture of anisole and n-butanol.

FIG. 1A

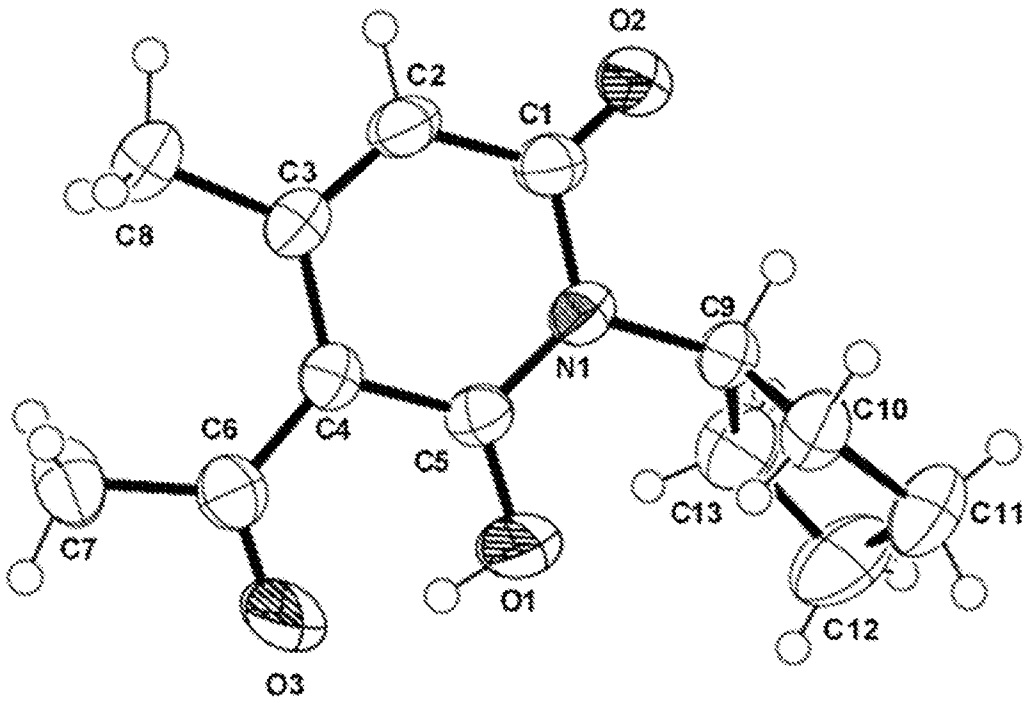
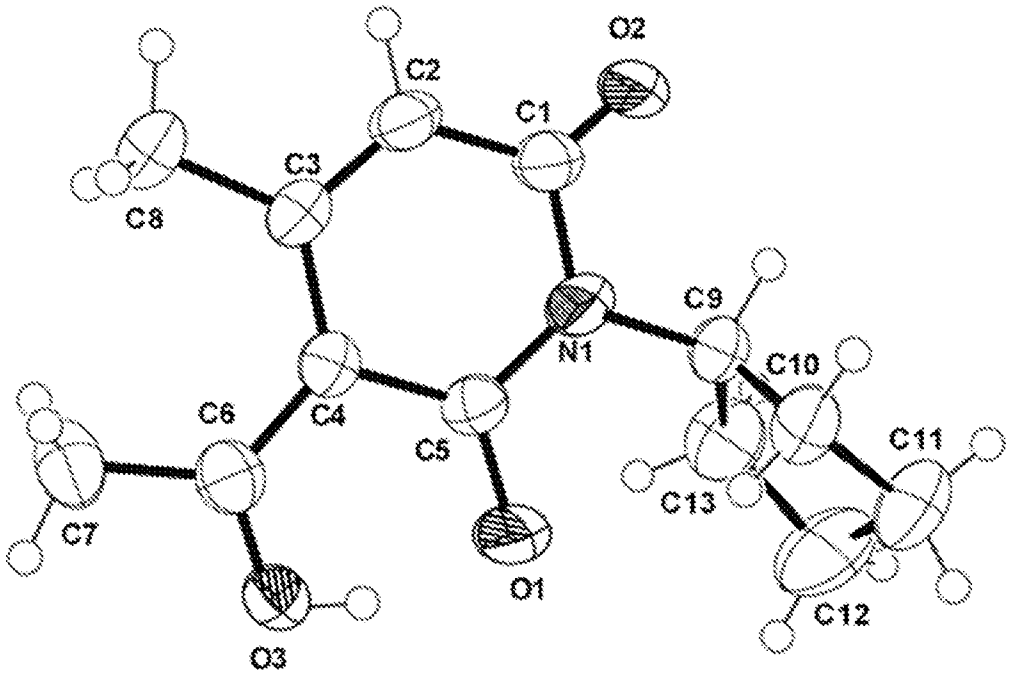


FIG. 1B



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/059991

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 3 186 252 A1 (RATIOPHARM GMBH [DE]) 5 July 2017 (2017-07-05)	21-27
A	page 7, step e2), formula 9 > formula 10; page 37, step e2); claims, e.g. Claims 6 and 7	1-20
	----- -/--	

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2022	24/01/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sen, Alina

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/059991

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VANDERWEL S N ET AL: "Pyrido[2,3-d]pyrimidin-7-ones as Specific Inhibitors of Cyclin-Dependent Kinase 4", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 48, no. 7, 3 February 2005 (2005-02-03), pages 2371-2387, XP002540183, ISSN: 0022-2623, DOI: 10.1021/JM049355+	15,21-27
A	the entire document, in particular page 2374, Table 3, compounds c and j; page 2377, Scheme 5, step iv; page 2384, "Experimental Section", compound 91 -> compound 31	1-14, 16-20
Y	TOOGOOD P L ET AL: "Discovery of a potent and selective inhibitor of cyclin-dependent kinase 4/6", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 48, no. 7, 7 April 2005 (2005-04-07), pages 2388-2406, XP002559229, ISSN: 0022-2623, DOI: 10.1021/JM049354H [retrieved on 2005-03-02]	15,21-27
A	page 2389, Scheme 1; page 2390, Scheme 3, compound (13) -> compound (14) and lines 2-4; page 2391, compound (36); page 2393, "Experimental Section" for compound (17)	1-14, 16-20
Y	US 2015/353542 A1 (DU ZHIMEI [US] ET AL) 10 December 2015 (2015-12-10) [0190]; [0191]; Example 5, in particular [0540]	15,21-27
Y	WO 02/062236 A1 (EDWARDS LIFESCIENCES CORP [US]) 15 August 2002 (2002-08-15) page 38, Scheme 4	15

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2021/059991

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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